

VOLUME 101 (5) — MAY 1992

1892

100th Anniversary

1992

Cuk-H03534-27-P024726

ANNALS

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RHINOLOGY &
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ANNALS OF HEAD & NECK MEDICINE & SURGERY

INSPIRATORY SPEECH AS A MANAGEMENT
OPTION FOR SPASTIC DYSPHONIA

TRANSMANDIBULAR TRANSPTERYGOID APPROACH
TO THE NASOPHARYNX, PARAPHARYNGEAL
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INSPIRATORY SPEECH AS A MANAGEMENT OPTION FOR SPASTIC DYSPHONIA

CASE STUDY

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A case study is reported of a subject who has used inspiratory speech (IS) for 6 years as a means of overcoming the communication problems of long-standing adductor spastic dysphonia (ASD). The subject was studied to confirm his use of IS, determine the mechanisms of its production, investigate its effects on ventilatory gas exchange, and confirm that it was perceptually preferable to ASD expiratory speech (ES). Results showed that the production and control of a high laryngeal resistance to airflow were necessary for usable IS. Voice quality was quantitatively and perceptually poor; however, the improved fluency and absence of phonatory spasm made IS the preferred speaking mode for both the listener and the speaker. Transcutaneous measurements of the partial pressures of oxygen and carbon dioxide in the subject's blood were made during extended speaking periods. These measurements indicated that ventilation was unchanged during IS, and that ventilation during ES was similar to the "hyperventilation" state of normal speakers. The reasons for the absence of phonatory spasm during IS are discussed, and the possibility of its use as a noninvasive management option for other ASD sufferers is addressed.

KEY WORDS — blood gases, inspiratory speech, spastic dysphonia.

INTRODUCTION

We report a case study of one of the authors (G.A.H.), who has used inspiratory speech (IS) for 6 years to the virtual exclusion of expiratory speech (ES) as a means of overcoming the communication problems associated with severe adductor spastic dysphonia (ASD). This voice is perceptually rough but fluent. The loudness is such that he has been able to resume teaching, public speaking, and other forms of vocal communication that were impossible with ES.

Although IS can be produced by anyone with a normal larynx,¹ there has been only one report² of an individual who developed IS of a quality consistent with occupational and social use.

We had a number of reasons for studying our subject: 1) we needed to confirm that IS was being used to the exclusion of ES; 2) we wondered if IS might be used to enable intelligible communication for other severe ASD sufferers, and felt that the effective teaching of IS would need to be based on an understanding of the behavior of the larynx and respiratory muscles during IS; 3) we wanted to feel confident that its long-term use did not result in any ventilatory or speech handicap; 4) we wanted to know whether listeners preferred IS to the subject's ASD ES; and 5) we felt that the absence of phonatory spasm in IS might increase our understanding of the neurophysiology of ASD.

Accordingly, we investigated the subject's phonation and ventilation in ES and IS. A perceptual

evaluation was carried out, and other relevant investigations were performed.

HISTORY OF SUBJECT'S DEVELOPMENT OF INSPIRATORY VOICE

The subject is a 58-year-old male medical practitioner. A voice disturbance was first noticed in 1982 during two attacks of an influenzalike illness. Within a few months, the subject's voice had the strained, groaning, staccato, effortful quality of established ASD. Phonatory blocks increased in frequency and after 18 months the fluency and intelligibility had deteriorated to the extent that the subject had to abandon teaching, public speaking, and use of the telephone. His vocational role was threatened by his inability to communicate effectively and even social communication was difficult except by whispering.

Two years after the onset of ASD, the subject started producing an occasional word on the deep inspiration required before attempting expiratory phonation. Within a few weeks his IS was fluent enough for social use. Since then, using IS, the subject has resumed teaching and public speaking.

CLINICAL CHARACTERISTICS OF EXPIRATORY VOICE AND RESPONSE TO INTERVENTIONS

The subject's ES is characterized by frequent vocal blocks, poor pitch control, and limited intensity. Some of the features have been reported previously³ (subject M1).

Relaxation techniques, deep hypnosis, ingestion of alcohol, and a variety of speech therapy maneuvers have had no effect on the quality of the ES. In

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Presented in part at the meeting of the Australian Association of Speech and Hearing, March 18-21, 1990.

the early stages, two techniques — stimulation of the nasopharynx by a catheter and delayed auditory feedback — caused transient return of the voice to normal. This response was lost as the disorder became more severe.

Lidocaine hydrochloride applied topically to the larynx by spray, inhalation after nebulization, or injection through the cricothyroid membrane produced little change in the voice, although early in the disorder, lidocaine 1.5 mg/kg injected intravenously produced a dramatic reversion to normal voice for 1 to 2 minutes. Injection of saline as a control produced no improvement. A more sustained but less complete improvement was maintained over several months with mexiletine hydrochloride (an oral antiarrhythmic related to lidocaine) administered at 200 mg three times daily. As the ASD became more severe, the response to intravenous lidocaine was lost and improvement with mexiletine could only be obtained with doses that produced gastrointestinal and central nervous system effects. The use of the drug was abandoned. The beta blocker metoprolol tartrate and the calcium channel blockers nifedipine and diltiazem hydrochloride did not affect the voice. Recurrent laryngeal nerve blocks with lidocaine or bupivacaine produced relief from the ASD for a few hours, but the voice was very breathy.

CLINICAL CHARACTERISTICS OF INSPIRATORY VOICE

The subject feels that he produces IS with no more effort than that which was required for ES before the onset of ASD. Conversation in loud background noise is difficult, but in a quiet room, over the telephone, or with amplification in a large lecture room, IS is normally fluent and appears very acceptable to listeners, although the voice is rough. During prolonged IS (eg, a lecture), the subject experiences a feeling of dryness in the throat and a need to clear the throat with one or two coughs at intervals of 5 to 10 minutes. During periods of intermittent speech, or during long periods of continuous speech when he is not under stress, the subject finds no difficulty in partitioning between breathing and speech. When under stress, such as in public speaking with time constraints, or when nervous, he reports some difficulty with ventilatory and phonatory partitioning, but has learned strategies to cope with this. The subject has no difficulty with IS during eating. No episodes of inhalation of food or liquids have occurred.

METHODS

LARYNGEAL EXAMINATION

The subject has undergone a number of direct and indirect laryngeal examinations using a transnasal fibroscope or a mirror.³ For the most recent examination the larynx was videotaped via transnasal fiberscopy while the subject used both IS and ES.

MEASUREMENT OF RESPIRATORY PARAMETERS

Phonatory Airflow. Airflow was measured by the use of a pneumotachograph and pressure transducer system (Vacumed mask, Mercury F100L flowhead, Hewlett Packard 270 differential pressure transducers, and Hewlett Packard 8805B amplifying system). The gas partial pressure of carbon dioxide (PCO₂) was measured with a Datex Normocap capnograph. The sample tubing was inserted through the mask so the tip lay in the respiratory gas stream. The voice signal was obtained from a throat microphone and a custom-designed circuit that produced the root-mean-square (RMS) energy of the waveform, and this was recorded simultaneously with airflow and PCO₂. The subject was asked to phonate the vowels "ah" and "ee" and to read the first paragraph of the Rainbow Passage using first IS and then ES.

Lung Volumes. Vital capacity and lung volumes were measured with an Emerson BP5 volume-displacement body plethysmograph calibrated by a 3-L syringe. The subject breathed through a Vacumed mask fitted to the external port in the clear plastic head dome. Lung volume and RMS voice energy were recorded simultaneously on a chart recorder out of the subject's vision. The subject first inspired and expired maximally to establish the vital capacity and this maneuver was repeated periodically. The subject read the Rainbow Passage in IS and repeated it in ES. In other tests he phonated vowels "ah" and "ee" for his maximum phonation time, starting at his functional residual capacity, and also from lung volumes above and below this. All tests were separated by brief rests outside the box. The modal lung volume was calculated from the recording by dividing the vital capacity into 10 ranges and allocating the recorded lung volume during reading to 1 of these ranges every 400 milliseconds. Respiratory rate was also noted.

Gas Exchange. The transcutaneous partial pressures of carbon dioxide (PtcCO₂) and oxygen (PtcO₂) were measured with a Radiometer TCM 20 carbon dioxide monitor and a Roche 335 transcutaneous oxygen monitor.

The electrodes were positioned on the skin over the superior surface of the shoulder after the skin was shaved, cleaned, and degreased with soapy water followed by alcohol. Sensor core temperatures were 44°C. The analyzers were allowed to stabilize for 20 minutes. The results were displayed on a chart recorder out of the subject's vision.

Four tests were conducted of the subject reading the Rainbow Passage in this order: IS (two sequential readings; 4 minutes total reading time), ES (two readings; 6 minutes), ES (two readings; 6 minutes), and IS (five readings; 10 minutes). The PtcCO₂ and PtcO₂ were allowed to return to control levels between each test.

Laryngeal Resistance. Transpulmonary pressure was measured with an esophageal balloon (length 10 cm, volume 0.5 mL) and a Statham PM131TC differential pressure transducer. Oral gas flow was measured with a Fleisch pneumotachometer (No. 2) connected to a differential transducer (Statham PM15ETC), and lung volume was obtained by electrical integration of the flow signal. Transpulmonary pressure, gas flow, and gas volume were recorded simultaneously (Mingograph 34). Static compliance and total pulmonary resistance were measured in tidal breathing by flow interruption and a computerized measurement system.⁴

The recording of transpulmonary pressure, gas flow, and gas volume was continued while the subject produced a sustained "ee" during IS or ES. Elastic recoil pressure at the chosen volume was calculated from 1) end tidal transpulmonary pressure and 2) the change in volume divided by static compliance.⁴ This value was subtracted (inspiration) or added (expiration) to the value recorded for transpulmonary pressure to give the total pressure across the airway.

PERCEPTUAL EVALUATION OF INSPIRATORY AND EXPIRATORY SPEECH

Sample tapes of the subject's IS and ES were played to 10 listeners. Five were speech pathologists with clinical experience in adult voice disorders and 5 were naive listeners. None of the 10 had any hearing impairment or neurologic disorder (by self-report).

A tape of the subject reading the first paragraph of the Rainbow Passage in ES and then IS was made in a quiet room. This tape was edited onto two further cassettes, one for ES and the other for IS. The two tapes were played to individual listeners in free field listening conditions at a preset comfortable volume. The order of playing the two types of speech (ES and IS) was reversed for half the group.

The listeners were not told the title and aim of the study until after they had completed the listening tasks. Instructions to listeners were standardized. Forced choice questions were administered individually, relating to each parameter: roughness, breathiness, strain, and severity.⁵ The parameter severity was chosen because IS does not produce a normal-sounding voice. After making their choices the subjects were asked which voice they preferred and why they preferred that voice. Presentation of the questions was randomized across all subjects.

Listeners repeated the listening task 1 week after the first presentation, and results on intrarater reliability were collated. Listener responses were collated independently by two of the authors, and no differences were found between their results.

PHONATORY CONTROL

Fundamental Frequency. Speaking fundamental

frequency (F0) was measured during reading of the Rainbow Passage. A throat microphone signal or a Fourcin laryngograph signal was processed by a time domain pitch meter, which has been previously described.⁶ In addition, the period of each cycle of the first sentence of the Rainbow Passage was determined manually by using the frequency calipers of a Le Croy 9400 digital storage oscilloscope. Phonational range was measured by having the subject match ascending and descending notes presented via headphones.

Intensity. The subject was asked to read the Rainbow Passage at a comfortable loudness, and in a quiet room, into a Bruel & Kjaer 2219 sound pressure level meter 30 cm from the mouth. A voltage output in decibels (using the A-weighted filter) from the sound pressure level meter was first linearized by a custom-build circuit, and then sampled into a microcomputer system described elsewhere.⁶ The output of the microcomputer represents the habitual intensity distribution of the subject during continuous speech. After or before the passage was read, a period of 10 to 15 seconds' silence was recorded to allow comparison of modal speaking intensity with ambient noise. The procedure was also performed in competition with background "babble" noise.

Timing and Articulation. The subject was asked to sustain "ah" for his maximum phonation time. For speech rate measurement the subject read the first paragraph of the Rainbow Passage at a comfortable speaking rate. Recordings of the reading passage were played and obvious signs of articulatory error, if any, noted. Words containing contrasting phonemes such as "p"/"b," and words containing the phoneme "h," which the subject considered to be more difficult to produce in IS, were also studied from a recording.

RESULTS

LARYNGEAL APPEARANCE

The larynx had a normal appearance at rest. During ES vigorous supraglottic adduction occurred that included closure of the ventricular folds and episodic apposition of the epiglottis to the aryepiglottic folds. On IS, the vocal folds approximated with a parallel glottic gap along the length of the vocal folds, estimated by the otolaryngologist at 1 to 2 mm; the posterior part of the glottis was mostly obscured, except in respiration, because of forward arytenoid tilt during phonation. The ventricular folds did not adduct at any time during IS.

MEASUREMENT OF RESPIRATORY PARAMETERS

Phonatory Airflow. Inspiratory airflow direction was confirmed. The average flow was approximately 100 mL/s for the prolonged vowel "ah" and 180 mL/s for a louder "ee" phonation. In Fig 1, the capnograph measure of PCO₂ increases to a peak of 33

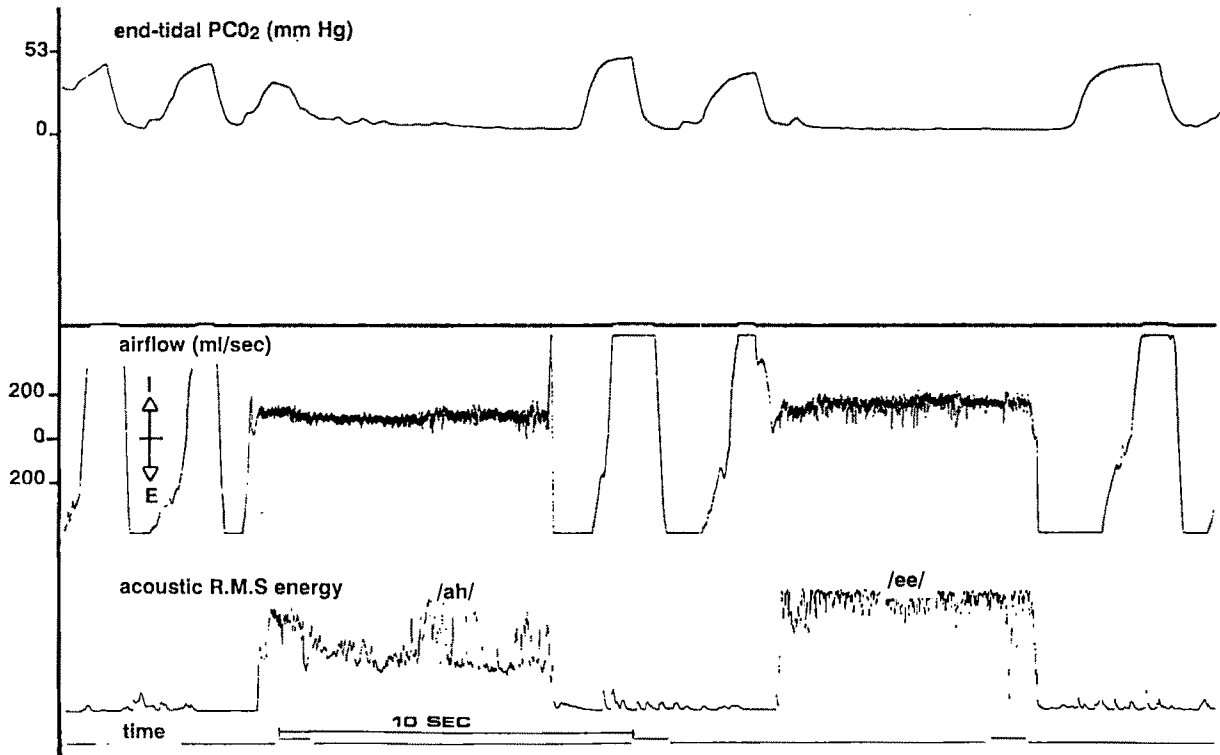


Fig 1. Capnograph measurement of carbon dioxide (PCO₂), oral airflow, and root-mean-square (R.M.S) acoustic energy during two prolonged vowels in inspiratory speech. I — inspiratory direction, E — expiratory direction.

mm Hg during the expiration preceding the first vowel prolongation and then declines toward 0 mm Hg as phonation proceeds, increasing to 50 mm Hg with the expiration after phonation.

During reading, the phonatory airflow was more variable, up to 400 mL/s; however, the inspiratory

flow appeared to be generally less than 200 mL/s. The PCO₂ during inspiratory flow declined to 3 mm Hg.

During ES for prolonged vowels "ah" and "ee" the airflow appeared to be similar to the 34-mL/s flow (range, 0 to 320 mL/s) previously reported for this subject for a similar task.³ The PCO₂ increased

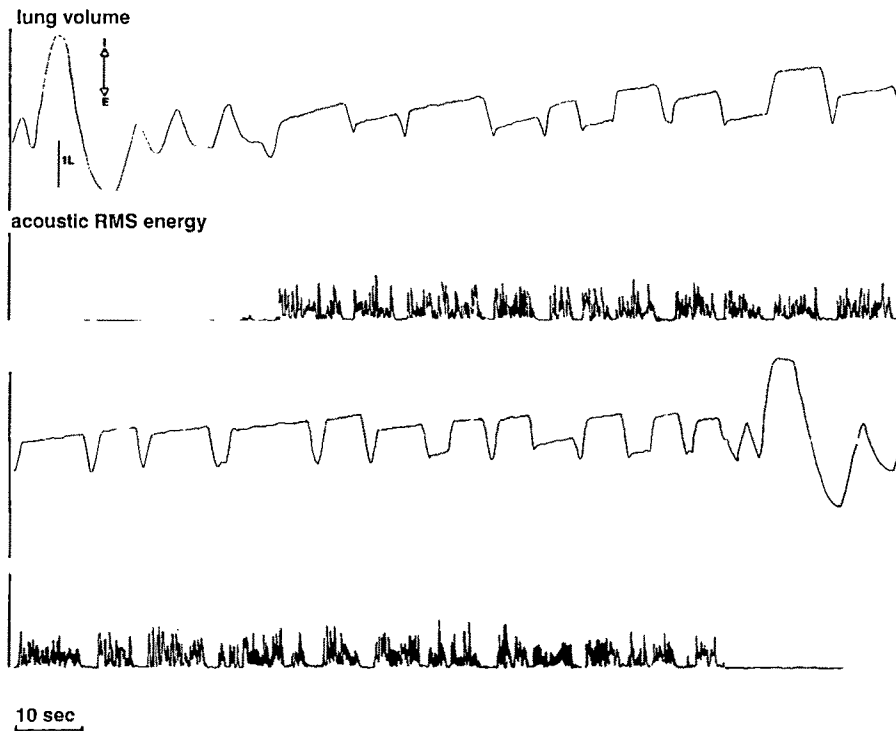
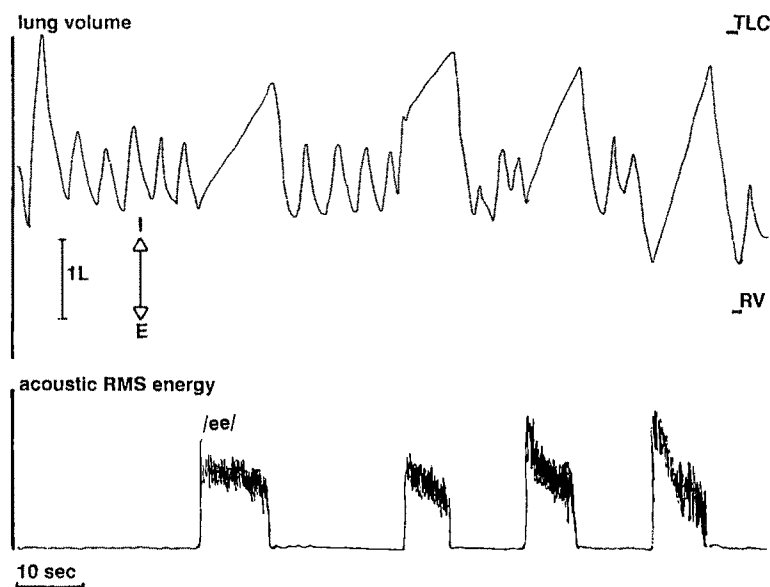


Fig 2. Lung volume and acoustic root-mean-square (RMS) energy during inspiratory speech reading of Rainbow Passage. Tracings are continuous from top to bottom. Vital capacity maneuver was performed at beginning and end of reading. I — inspiration, E — expiration.

Fig 3. Lung volume and acoustic energy of sustained vowel during inspiratory speech. Phonation initiated at end tidal, high, end tidal, then low lung volumes and separated by tidal breathing. I — inspiration, E — expiration, RV — residual volume, TLC — total lung capacity, RMS — root-mean-square.



gradually to a peak of 47.4 mm Hg during the vowel prolongation.

Lung Volumes. There were two general patterns of lung volume during IS reading (Fig 2). First, from near the tidal range, the subject would speak for several seconds, and then quickly expire a volume approximately equal to the tidal volume, followed by an inspiration to the level at which speaking had just ceased. He would then start speaking again at that volume. Alternatively, he would speak for several seconds, expire and speak at the lower lung volume for several seconds, then inspire and continue speaking at a new, higher lung volume. Figure 3 shows that IS could be initiated over a range of lung volumes. Respiratory variables, including respiratory rate and lung volume ranges used during IS and ES, are given in Table 1. The subject's vital capacity was measured as 3.46 L. This was 101 % of predicted.

TABLE 1. RESPIRATORY VARIABLES IN SUBJECT WITH ADDUCTOR SPASTIC DYSPHONIA

	Expiratory Speech (Reading*)	Inspiratory Speech (Reading*)	Quiet Breathing
Respiratory rate (breaths per minute)	9.5	10.4	12.0
Speaking rate (syllables per minute)	85	213	—
Speech initiation lung volume (mean % vital capacity)	90.1 (SD 9.5)	51.4 (SD 10.4)	—
Speech termination lung volume (mean % vital capacity)	50.9 (SD 11.5)	57 (SD 9.3)	—
Modal lung volume (% vital capacity)	75	55	38
PtcO ₂ (mm Hg)	88.5	78.9	77-79
PtcCO ₂ (mm Hg)	35.5	40.3	40-40.5

Dash — data not applicable.
*Over entire Rainbow Passage.

Gas Exchange. The subject's ventilation during IS (as judged by the transcutaneous gas measurements) was very similar to nonphonatory breathing (Table 1). During the subject's ES the PaCO₂ dropped 4.5 mm Hg, which seems to represent the typical variation during normal ES.⁷

Laryngeal Resistance. During tidal breathing, pulmonary compliance was 0.176 (SE 0.007) L/cm H₂O; total pulmonary resistance during inspiration was 2.4 (SE 0.2) cm H₂O/L per second, and during expiration it was 3.1 (SE 0.2) cm H₂O/L per second. During a sustained "ee" in IS, lung volume was 300 mL above the end tidal level, net gas flow across the larynx was 100 mL/s, and total pressure across the airway in four trials was 24, 28, 24, and 27 cm H₂O. This implies a laryngeal resistance of more than 250 cm H₂O per second.

During ES, volume initially increased by 600 mL above the end tidal level, and net expiratory flow was approximately 100 mL/s. The total pressure

TABLE 2. PERCEPTUAL EVALUATION OF SUBJECT'S INSPIRATORY AND EXPIRATORY VOICE

	More Breathy		More Rough		More Strained		More Severe		Preferred	
	E	I	E	I	E	I	E	I	E	I
n1	X			X	X			X		X
n2	X		X		X		X			X
n3*		X	X		X		X			X
n4*	X		X		X		X			X
n5*	X		X		X		X			X
e1	X			X	X		X			X
e2	X		X		X		X			X
e3	X		X		X		X			X
e4*	X			X	X		X			X
e5*	X			X	X		X			X

Responses of five naive listeners (n1 through n5) and five experienced speech pathologists (e1 through e5) are depicted. Intrarater reliability was 99 %.

Crosses indicate which voice, either inspiratory (I) or expiratory (E), is best described by column heading.

*Reverse order of presentation.

gradient across the airway during 10 seconds of recording was in the range of 21 to 31 cm H₂O. Laryngeal resistance was therefore similar to that calculated for IS.

PERCEPTUAL EVALUATION

All listeners, naive and experienced, preferred listening to IS (Table 2). In addition to the forced choice questions, the listeners had been asked to comment as to why they preferred the speech sample they had chosen. Terms describing ES that occurred frequently were "strain," "effort," "struggle," "irritating sound," "disrupted," and "feeling uncomfortable." Terms describing IS occurring with most frequency were "better fluency," "higher speed," "less discomfort," "less hesitation," "better rhythm," and "more consistency." One naive listener commented, "The first voice (ES) makes the listener feel uncomfortable — instead of listening to what the first speaker is saying you feel anxious about his difficulty in bringing the words out."

Point-by-point intrarater reliability was 99%: only one listener changed her answer the following week. The best reliability occurred on the parameters strain, severity, breathiness, and preference. The poorest reliability was for roughness: four listeners chose IS and six chose ES.

PHONATORY CONTROL

Fundamental Frequency. Expiratory speech showed a modal speaking F₀ of 150 Hz (range, 50 to 260 Hz), and although the range is high, the modal F₀ is within normal limits.⁶

For IS, the F₀ distribution was almost completely below 100 Hz, and below normal limits. The acoustic wave was characterized by gross perturbations in both period and amplitude, and there were intermittent occurrences of falsettolike phonation with F₀ on the order of 500 Hz. The hand measurement of the first sentence of the Rainbow Passage (in IS) returned a modal F₀ of 80 Hz. There were also episodes of relative stability in the wave, but these were transient.

Phonation range during note matching was 69 to 510 Hz (35 semitones) for phonations sustained for periods longer than 1 second.

Intensity. The modal speaking intensity during reading in IS in a quiet room was 61 dB (range, 50 to 64 dB). The background noise was measured at 45 dB. When asked to read as loudly as possible, the subject achieved a modal intensity of 79 dB (range, 73 to 85 dB). However, when asked to read in competition with a recorded noise of 80 dB (range, 76 to 84 dB), comprising the summed voices of a number of people ("babble" tape), the modal intensity of "babble" plus subject was 82 dB, ie, the subject's intensity was slightly lower than background.

During ES the modal intensity was 67 dB (range,

55 to 73 dB) against a background of 45 dBA. Maximum intensity was 78 dB (range, 68 to 83 dB) with no background competition, and again 82 dB against the "babble" noise.

Timing and Articulation. The subject's comfortable reading rate for IS was a normal 213 syllables per minute,⁸ but for ES, only 85 syllables per minute (Table 1). He was able to read more quickly and also more slowly in IS than in ES. His maximum phonation time was 17 seconds for both IS and ES.

He has no trouble being understood. Some phonemes would logically be thought to be difficult to produce in IS, such as the voiceless plosive "p" and "h," especially in initial positions. A voiced-voiceless contrast was clearly heard by two of the authors (P.J.D., A.L.W.) between minimally paired words when presented together, eg, "batch/patch." However "batch" was heard as "patch" when presented alone. This finding suggests that the subject compensates for reduced articulatory intelligibility but cannot compensate fully, and the listeners use word context and contrast, when necessary, to understand. The phoneme "h" was clearly perceived as expiratory in initial position in isolated words.

DISCUSSION

We have shown that our ASD subject uses IS and produces it at a useful intensity. It can be learned by individuals with normal voices, as one author (R.H.T.) has done. We do not know if it is possible for IS to be applied therapeutically to other patients with ASD. Even if it is, it may not be suitable for some of the subgroups that have been identified in ASD.^{3,9} Those ASD patients for whom vocal tremor or dystonia is significant may find it difficult to learn the new motor speech behavior for IS. Further, whether it is likely to be useful to an individual patient with ASD depends on a number of variables. It may be appropriate to judge the potential value of IS on a need-performance ratio of the voice in any patient's particular social and occupational roles, as well as the potential complications or difficulty in learning IS. For an individual "mild" ASD may be more acceptable than IS. In the case of the subject described, the need for effective vocal performance was very high, while the quality of ASD ES speech was very low. Intervention with IS had the attraction that it was noninvasive, easily acquired, and, although not normal-sounding, was surprisingly acceptable in most social and occupational situations, except those with high ambient noise levels.

Despite a small amount of disagreement among listeners in the perceptual study about roughness and, to some extent, severity, all listeners agreed that they preferred listening to IS. The preference appeared to be due to characteristics other than voice quality. Most listeners mentioned fluency and other associated concepts to explain their prefer-

ence, and indeed IS was markedly more fluent than ES, with more than double the maximum speech rate. There are large cycle-by-cycle variations in amplitude and period in the IS voice waveform, and these are likely to be major contributors to the perceived roughness of the IS voice. In addition, the lower frequencies may also contribute to poor sound quality in that the fundamental periods are often long enough for the energy in the vocal tract to die out between individual cycles, giving the voice a pulslike quality.¹⁰ Certainly the naive listeners may have had problems assigning quality parameters such as "severity," "roughness," etc, because they felt unqualified to make such judgments, even though it was stipulated that their opinion only was required.

The subject has found IS more comfortable than ES. This accords with our observation that the lung volume range from which IS was initiated was similar to that reported for normal adults¹¹ (Table 1). Inspiratory speech was usually produced at a lung volume similar to the tidal breathing range, where the elastic forces in the lungs and chest wall are comfortably balanced. Conversely, the discomfort and fatigue experienced with ES are likely to be associated with the high lung volumes at which the latter occurs, although the elevated lung volumes would assist in overcoming the phonatory adductor spasm in ES because of the higher pressure that can be generated by the increased mechanical advantage of the expiratory muscles and the greater elastic recoil of the lungs. Additionally, the abdominal muscles are regularly recruited at high lung volumes,¹² and their contraction is capable of generating high pressure in the lungs against a closed glottis, particularly at high lung volumes. It is also possible that there are prolonged periods of elevated cerebral venous pressure during the Valsalvalike maneuvers of the ES vocal blocks.

In IS the nonphonated rapid inspirations preceding a slower phonated inspiration may be necessary for ventilation, as the slow inspiration may not produce gas exchange. The nonphonated rapid expirations after each phonatory period are presumably associated with the need for CO₂ excretion. Bunn and Mead⁷ also observed nonphonated expirations in reading subjects who were exposed to 3.5% CO₂ in air rather than air alone.

The subject was able to generate and maintain a 25- to 30-cm H₂O pressure drop across the glottis with a net inspiratory flow. Leanderson et al¹³ found that singers consistently used their diaphragms when they needed to rapidly decrease subglottic pressure during singing. On this basis, it may be that our subject has learned to voluntarily control the activity of his diaphragm and/or intercostal muscles in a manner consistent with the habitual use of sustained inspiration associated with (in respiratory terms) very low flows against a high la-

ryngeal resistance.

Our subject has also acquired a different pattern of laryngeal control. Moore and von Leden¹ observed inspiratory phonation in high-speed motion cinematography. They observed vibration of the membranous part of the vocal folds, with variation in the amplitude of cord vibration from cycle to cycle, and phase differences often occurring in the lateral motions of the two cords. In the present study, the vocal folds did not fully approximate, and although we were not able to view the posterior glottis at all times during connected speech, the observed gap between the membranous part of the folds was probably associated with a posterior opening of the glottis. This pattern of activity is very different from that which normally occurs on inspiration, in which the vocal folds vary in abduction depending on ventilatory demands.

These observations suggest two explanations that may account for the observed fluency in IS but not ES. First, each respiratory phase is associated with a centrally determined recruitment of different laryngeal muscles. Expiratory phonation is generally associated with activity in the laryngeal adductor muscles: thyroarytenoid, lateral cricoarytenoid, and interarytenoid. Inspiration is marked by the contraction of the abductor muscle, the posterior cricoarytenoid, which starts contracting at the same time or slightly ahead of the diaphragm.¹⁴ Selective voluntary control of the posterior cricoarytenoid to the extent of inhibiting this inspiratory contraction is unlikely. Its involuntary contraction during IS may therefore be a counter to the spasm in the adductor laryngeal muscles. The resultant sum of adduction-abduction forces in the larynx may then result in a gentler approximation of the vocal folds.

An alternative explanation may be linked to recent demonstrations that laryngeal activity during breathing in humans and animals is controlled by reflexes involving lung volume and pressure.^{14,15} If such reflex control could be shown to exist in vocalization, then the absence of the phonatory spasm on IS, associated with the maintenance of negative lung pressures, and its presence in ES in which positive pressures are generated, could at least suggest the possibility that respiratory reflexes involving the larynx may be abnormal in some persons with ASD.

There have been relatively few reports of successful treatments that might be carried out by speech pathologists, or reports of alternate methods of communication that might be of interest to individuals with severe ASD.¹⁶ The section of one recurrent laryngeal nerve¹⁷ was introduced to minimize the degree of adductor spasm, and this procedure has produced an improved voice for a number of patients. However, this procedure is not without risk,¹⁸ and long-term follow-up studies indicate an overall recurrence rate of 64%.¹⁹ More recently, injection

of botulinum toxin into the laryngeal adductor muscles^{20,21} has been successful in restoring normal voice in a number of published cases, although it may not be suitable for all ASD patients.²¹ The subject of this paper developed IS before the reports on botulinum toxin were published. He has chosen to continue with IS because of its normal fluency and near-normal intelligibility and utility. He accepts that the voice has a quality somewhat like that of moderate laryngitis.

Although inspiratory phonation occurs in some languages on at least some words,²² IS is not common, and for this reason has probably not been viewed seriously as a management option. It may be possible in the future to offer IS or botulinum toxin to patients whose ASD voice is unacceptable to them in their social or vocational roles. The option would be between a voice that is rough but use-

ful and a voice that would perhaps be more normal-sounding but have uncertain longevity.

The results of the studies of airway resistance, ventilatory control, and phonatory control have implications for the teaching of IS. We have noted that individuals attempting IS for the first time use a very high airflow. We observed that our subject creates a high pressure drop across the glottis and a low flow rate during IS that indicates that laryngeal resistance is high. The author without ASD who learned IS (R.H.T.) found that he needed to develop these controls of flow and resistance before he could produce acceptable IS, which seems to require new learned control of the diaphragm and abdominal, intercostal, and laryngeal muscles. However, the learning of this control has not proved excessively difficult to the two authors, and it may be that the learning of IS is a relatively simple exercise.

ACKNOWLEDGMENTS — We gratefully acknowledge the assistance of Prof H. J. H. Colebatch of the Department of Respiratory Medicine, University of New South Wales, in the measurements and interpretation of laryngeal resistance values; Lina Lee, St Vincent's Hospital, in setting up and calibrating the transcutaneous blood gas measurements; and Felicity Carter in preparing the manuscript.

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TRANSMANDIBULAR TRANSPTERYGOID APPROACH TO THE NASOPHARYNX, PARAPHARYNGEAL SPACE, AND SKULL BASE

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The nasopharynx, upper part of the parapharyngeal space, and skull base are relatively inaccessible to the surgeon without major postoperative complications. Operative fields reached by conventional approaches through the palate and maxillary sinus are too limited and narrow to remove extensive tumors. The authors applied a transmandibular transpterygoid approach for the removal of five residual nasopharyngeal carcinomas (NPCs) after full doses of irradiation, one pleomorphic adenoma of the nasopharynx, and one large parapharyngeal schwannoma extending into the jugular foramen. This approach offers a wide operative field so that large blood vessels and cranial nerves can be managed easily. All tumors were successfully resected. Two patients with benign neoplasms had uneventful recoveries after treatment. Of five patients with NPC, two are alive with no evidence of disease for 68 months and 50 months, respectively, while two died of metastases to the liver and bones. The other patient is alive with metastases in the lungs. No tumor recurred in the local primary site, however. Since the number of NPC cases is small, the usefulness of surgical removal of the postirradiation residual NPC is not clear. Our experience proved that the transmandibular transpterygoid approach is a practical method in the treatment of neoplastic lesions in the nasopharynx, parapharyngeal space, and skull base.

KEY WORDS — jugular foramen, nasopharynx, parapharyngeal space, schwannoma, skull base, transmandibular transpterygoid approach.

INTRODUCTION

Nasopharyngeal cancer (NPC) has a relatively poor prognosis compared to carcinomas arising from other head and neck regions. In fact, the 5-year survival rate has been reported as between 29% and 46%.¹⁻⁴ Radiotherapy is the choice for treating NPC because most NPC is very sensitive to irradiation. A primary lesion very often disappears after this therapy. Recent advances in imaging the exact extent of tumor invasion — computed tomography (CT) and magnetic resonance imaging (MRI) — provide reliable means for making an accurate diagnosis and assessing the effects of treatment. Huang⁵ reported improved radiotherapy techniques for NPC resulting from his more accurate diagnosis of the extent of NPC with the aid of CT scanning. The authors have also applied radiotherapy as a primary treatment for NPC, using CT scans as a major means of follow-up during and after radiotherapy since 1982. The results showed that NPC did not always disappear after 60 Gy of irradiation, even when posterior rhinoscopic or flexible fiberoptic observation did not indicate residual tumor. Therefore, we performed surgical treatment to eradicate such residual tumors through a transmandibular transpterygoid approach. This approach is indicated for NPC extending to the parapharyngeal space. The experience with these cases prompted us to apply the technique to remove extensive benign neoplasms in the nasopharynx, parapharyngeal space, and skull base. One patient with pleomorphic adenoma extending from the nasopharynx to the parapharyngeal space and five patients with postirradiation residual tumor of NPC were oper-

ated on. We surgically treated a patient with a large parapharyngeal schwannoma arising from the vagus nerve and entering the posterior cranial fossa through the jugular foramen. The purpose of this paper is to describe an operative procedure performed via the transmandibular transpterygoid approach to the nasopharynx and upper part of the parapharyngeal space and to show the usefulness of this method from case results.

PATIENTS

Between February 1985 and January 1990, seven patients were operated on by the transmandibular transpterygoid approach. Table 1 summarizes age, sex, histology, and extent of tumor of the seven cases. Patients 1 to 5 suffered from NPC, patient 6 had pleomorphic adenoma of the nasopharynx, and patient 7 had a large vagus nerve schwannoma in the upper part of the parapharyngeal space. The

TABLE 1. PATIENT AGE, SEX, HISTOLOGY, AND EXTENT OF TUMOR

Patient	Age	Sex	Histology	Extent of Tumor*
1	42	M	SCC	T2N2c
2	68	M	SCC	T3N0
3	41	M	SCC	T3N2c
4	40	M	SCC	T2N2c
5	55	F	ACC	T3N0
6	54	F	Pleomorphic adenoma	Nasopharynx to upper parapharyngeal space
7	33	M	Schwannoma	Upper parapharyngeal space to jugular foramen

SCC — squamous cell carcinoma, ACC — adenoid cystic carcinoma.

*Based on 1987 UICC classification.

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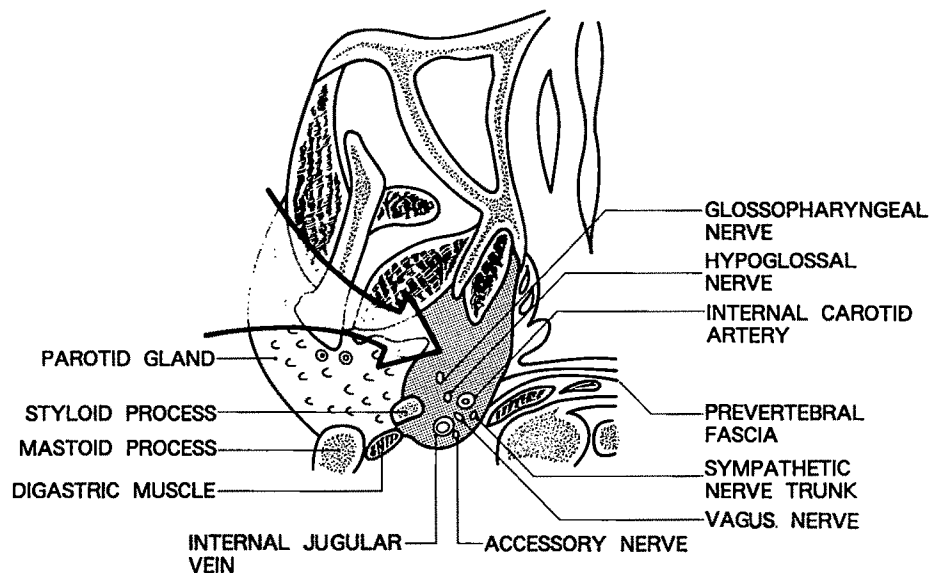


Fig 1. Anatomy of parapharyngeal space (dotted area) and nasopharynx. Poststyloid compartment of parapharyngeal space includes large vessels and several cranial nerves. Arrow — direction of transmandibular transpterygoid approach.

histology of four NPC cases (patients 1 to 4) indicated squamous cell carcinoma, two being moderately differentiated (patients 2 and 3), and the other two, poorly differentiated (patients 1 and 4). The histology of case 5 showed adenoid cystic carcinoma.

SURGICAL PROCEDURE

Figure 1 illustrates the anatomic relation of the upper part of the parapharyngeal space and the nasopharynx. The large arrow in Fig 1 shows the direction of this approach. Temporary tracheostomy is necessary for maintaining an airway during the immediate postoperative period. A skin incision divides the lower lip in the midline and continues down through the chin. The incision then curves downward across the neck and up in front of the ear as shown in Fig 2A. A mucosal incision is made from the corner of the lip incision, proceeding posteriorly along the lower gingivolabial sulcus. The incision crosses the ascending ramus of the mandible and ends close to the pterygoid hamulus (Fig 2B). A vertical skin incision may be made when neck dissection is necessary. Soft tissues including skin, the masseter muscle, and the parotid gland are elevated from the mandible and retracted upward.

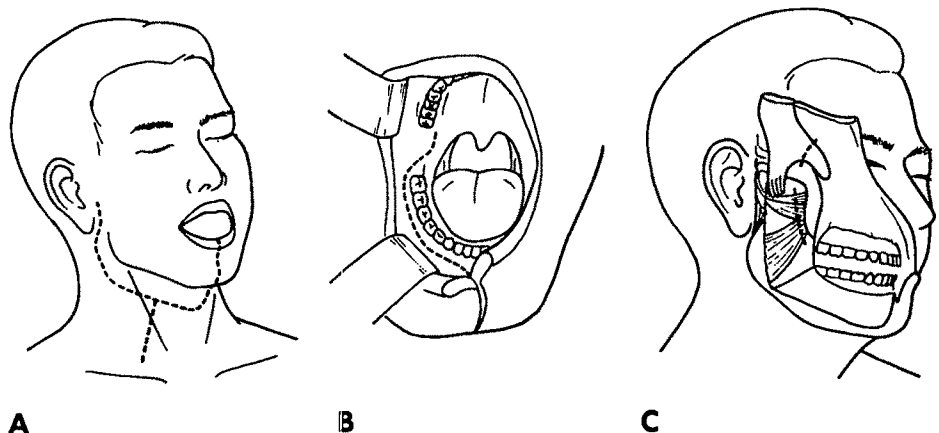
This step preserves the facial nerve function completely. The mandible is cut just posterior to the third molar tooth. The ascending ramus of the mandible is then retracted upward. Resection of the coronoid process greatly facilitates mobility of the ascending ramus and helps prevent postoperative trismus. The exposed lateral and medial pterygoid muscles are divided in order to reach the lateral wall of the nasopharynx (Fig 2C). The identification of large vessels in the upper neck and following them upward to the skull base are key points in this operation.

A small mucosal defect of the nasopharynx after tumor removal may be left without epithelial lining. Dead space left after large tumor resection is filled with the pterygoid muscles or a pedicled sternocleidomastoid muscle. The internal carotid artery is protected by these muscles. The retracted ascending ramus assumes its original position and is fixed by the miniplate method (Martin Co). The tracheostoma is terminated several days after the operation.

CASE REPORTS

Patient 2. A 68-year-old man had occasional

Fig 2. Schematic drawing of surgical procedure. A) Skin incisions. B) Incision of oral mucosa. C) Approach to nasopharynx made by retracting ascending ramus of mandible and soft tissues upward.



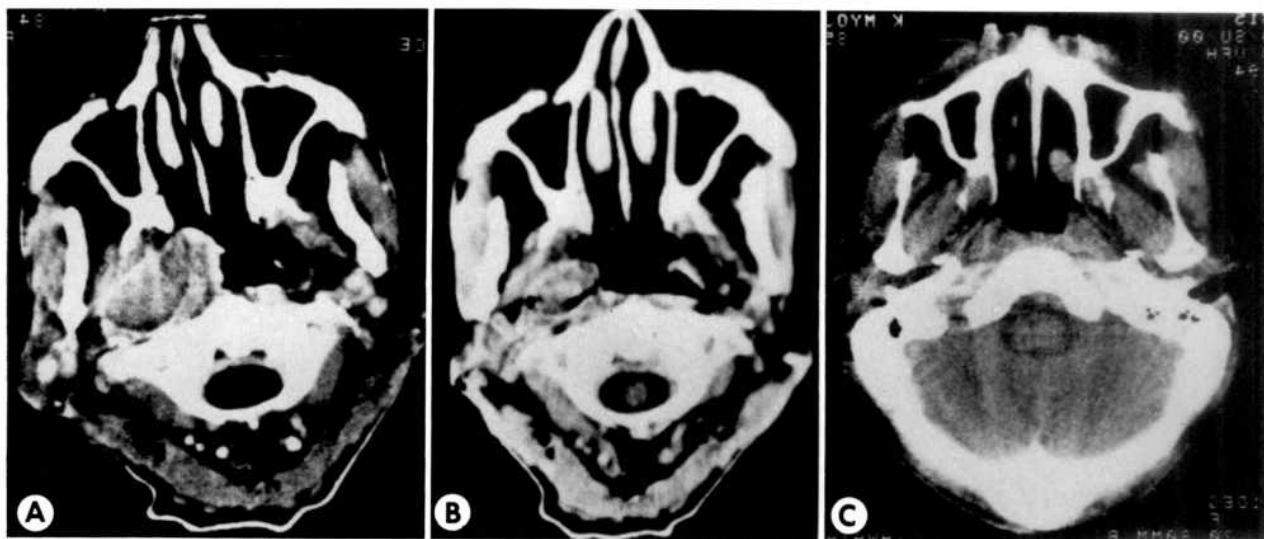


Fig 3. (Patient 2) Computed tomograms. A) At initial visit (before irradiation). B) Two weeks after 60 Gy irradiation. Tumor did not disappear. C) No evidence of residual tumor 5 months after operation.

bloody sputum for half a year. Because of increased frequency of bloody sputum, he went to a hospital and was found to have a nasopharyngeal tumor. A biopsy specimen was taken and the case was diagnosed as moderately differentiated squamous cell carcinoma. He was subsequently referred to our hospital on November 26, 1984. The right lateral wall of the nasopharynx bulged into the cavity, and CT showed tumor invasion into the parapharyngeal space (Fig 3A). Two weeks after 60 Gy of irradiation to the nasopharynx and neck, CT clearly detected a residual tumor extending from the nasopharynx to the parapharyngeal space (Fig 3B). Surgical tumor removal through a transmandibular transpterygoid approach and right conservative neck dissection were performed 1 month after irradiation. The tumor lay posterior and superior to the opening of the eustachian tube and adjoined the internal carotid artery (Fig 4). It was removed en

bloc. Histologic examination indicated viable malignant cells. The patient has had no evidence of disease for 68 months. In Fig 3C, CT findings 5 months following the operation are shown.

Patient 5. A 55-year-old woman noted left nasal obstruction 2 years prior to her first consultation. She was histologically found to have adenoid cystic carcinoma occupying the left nasal cavity and left side of the nasopharynx and invading the pterygoid fossa and parapharyngeal space (Fig 5A). Radiotherapy was quite effective. Figure 5B shows remarkably decreased tumor size 2 weeks after 60 Gy of irradiation. On February 16, 1988, the residual tumor was removed by a transmandibular transpterygoid approach in combination with a transmaxillary approach. The tumor invaded the internal pterygoid and longus colli muscles. The ascending ramus of the mandible was removed with the

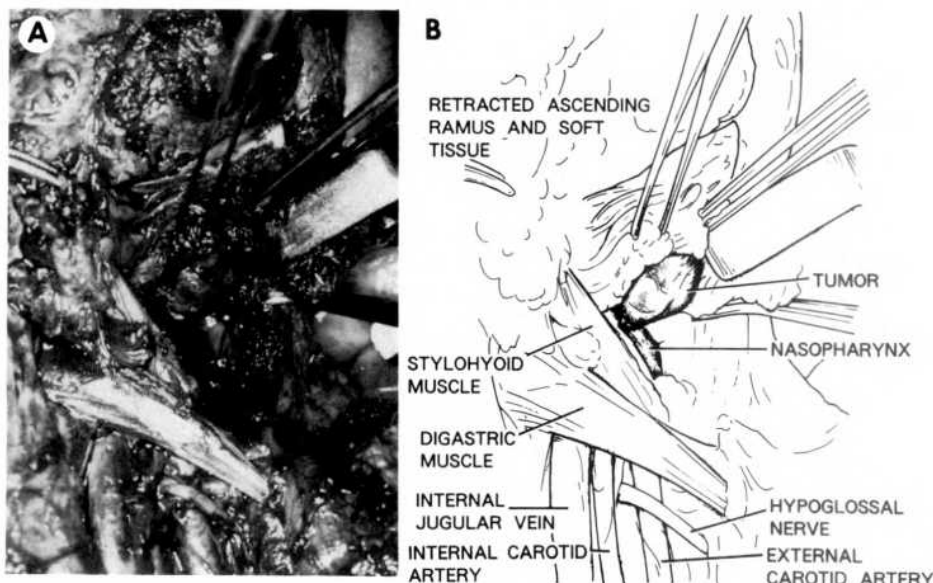


Fig 4. (Patient 2) Tumor lies posterior and superior to opening of eustachian tube and adjoins internal carotid artery. A) Operative findings. B) Schematic illustration.

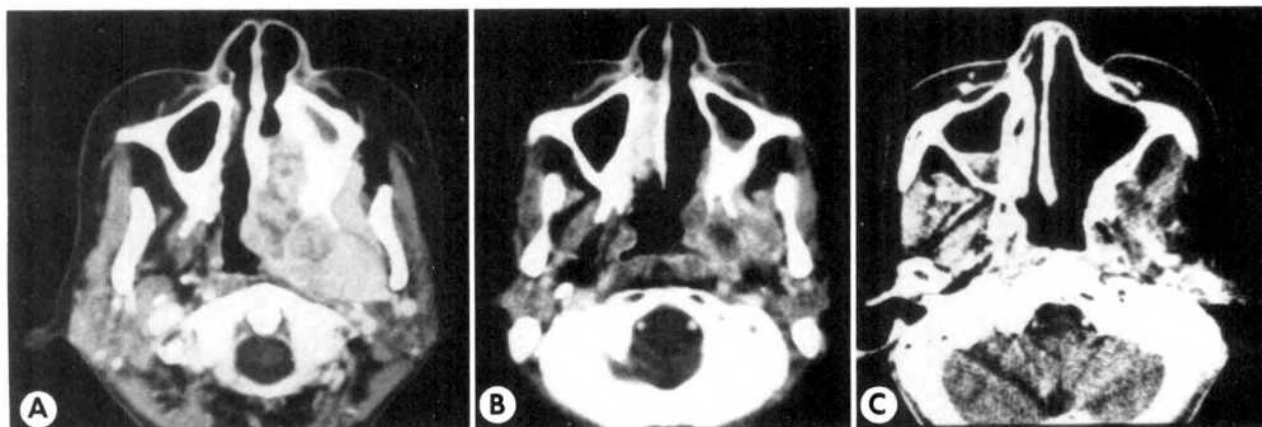


Fig 5. (Patient 5) Computed tomograms. A) Tumor of substantial size at initial consultation (before irradiation). B) Two weeks after 60 Gy irradiation. Radiotherapy was quite effective and tumor size remarkably decreased. C) No residual tumor 8 months after operation.

tumor. Histologic examination showed viable malignant cells. Figure 5C shows a CT scan indicating no local tumor 8 months after the operation. Two years later, the patient was found to have small coin lesions in the lung, although the primary site remained free of disease.

Patient 7. A 33-year-old man had noticed slowly progressive palsy of the tongue and soft palate on the left side for a few years. A CT examination clarified a large tumor in the left parapharyngeal space. An MRI scan showed the tumor to extend to the posterior cranial fossa through the jugular foramen, as shown by white arrows in Fig 6B. The internal ca-

rotid artery, indicated by black arrows in Figs 6B and 7A, was shifted anteriorly to the tumor. The venous phase of left internal carotid artery angiography showed no blood flow in the lateral sinus or internal jugular vein of the affected side (Fig 7B). Schwannoma arising from the vagus nerve was considered to be quite possible. On January 23, 1990, the patient was successfully operated on through a transmandibular transpterygoid approach. Intraoperative histologic examination with frozen section indicated benign schwannoma. Figure 8 presents a macroscopic picture of the totally removed tumor. There was a leak of cerebrospinal fluid from the jugular foramen. Doubly placed fascia lata,

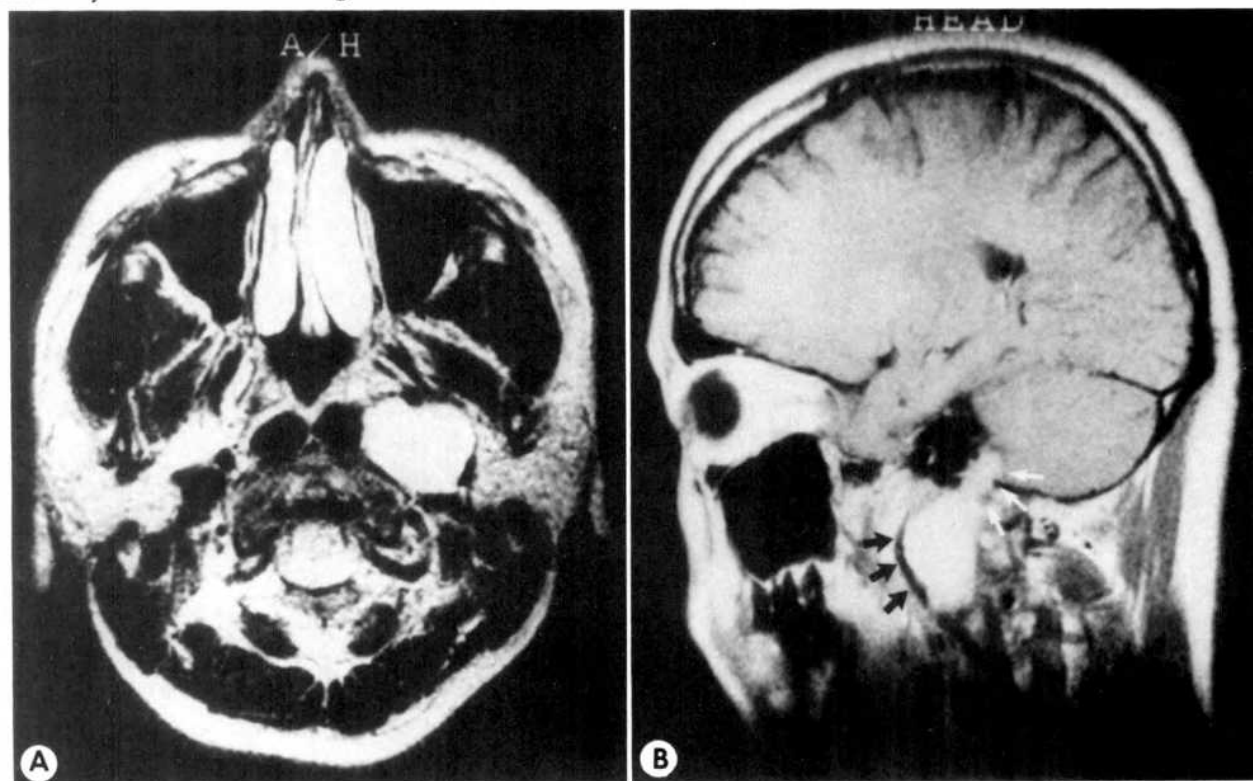


Fig 6. (Patient 7) Magnetic resonance images. A) Large parapharyngeal tumor. B) White arrows — extension to jugular foramen, black arrows — internal carotid artery that has shifted anterior to tumor.

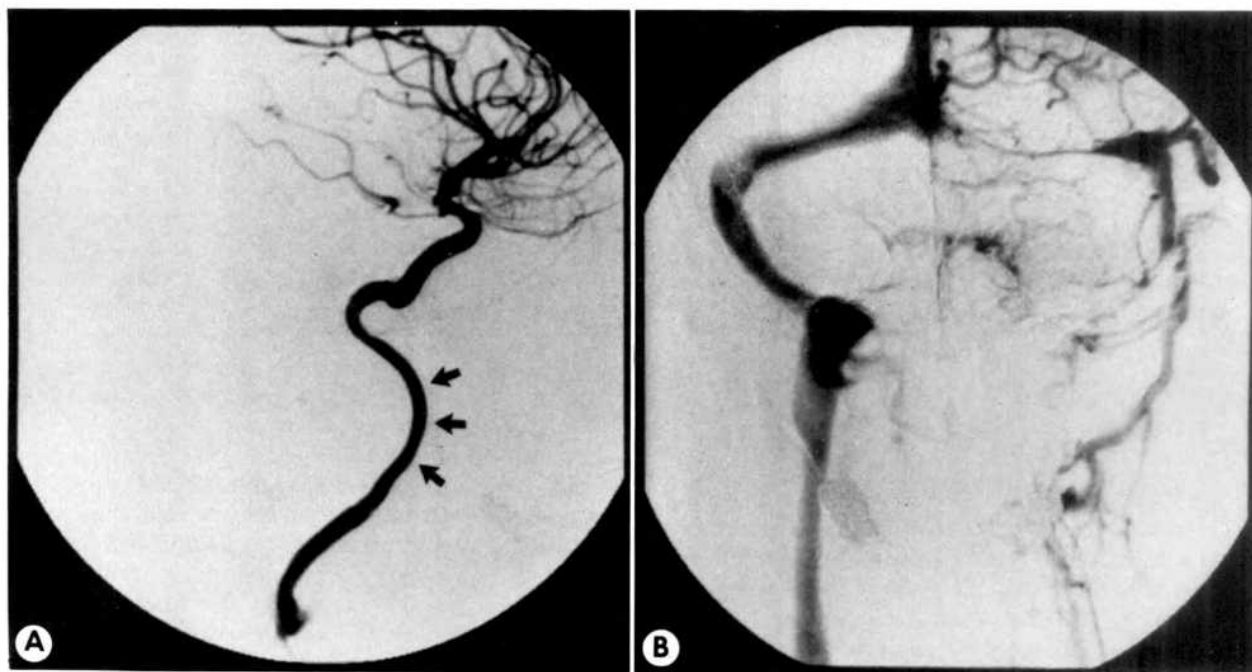


Fig 7. (Patient 7) Angiograms obtained by digital subtraction. A) Internal carotid artery (arrows) was shifted anterior to tumor. B) Venous phase of left carotid angiography shows no blood flow in lateral sinus or internal jugular vein of affected side.

sealed with bioactive adhesive and masses of fat, was useful in stopping the leak. The patient has been asymptomatic since then.

RESULTS

Table 2 lists the outcomes of the five NPC cases. Patients 2 and 4 have been asymptomatic for 68 and 50 months, respectively. Patients 1 and 3 died of multiple metastases to the liver and/or bone 4 years and 6 months after treatment, respectively. Patient 5 is alive, but was found to have multiple metastases to the lung 2 years after treatment. The three patients with distant metastases (1, 3, and 5) had no tumor in the primary site, however.

Table 3 indicates the intraoperative blood loss and postoperative sequelae of all seven cases. Blood loss ranged from 100 mL in patient 7 to 1,070 mL in patient 3, with a mean of 589 mL. Three patients (2, 3, and 5) did not have any sequelae after the operation. In patient 7, removal of the tumor resulted in palsy of the recurrent nerve, since the tumor was a schwannoma arising from the vagus nerve. Patients 1 and 6 showed paresis of the soft palate that improved later, but not completely. These two patients did not experience swallowing difficulty. Their only symptom was nasality of speech. Infection of the mandible at the temporarily resected site in patient 4 occurred 2 months after the operation. Conservative treatment with pus drainage and local antibiotics failed to improve the infection. The infected bone and miniplate were removed surgically, allowing the wound to heal. All patients except patient 4 were able to open the mouth sufficiently for eating, as shown in Fig 9.

COMMENTS

The nasopharynx, parapharyngeal space, and skull base are areas in which it is difficult to detect pathologic changes. Recent advances in diagnostic methods such as CT scanning and MRI have made it possible to rather clearly determine the extent of neoplasm in these areas. Huang⁵ reported that he could determine the correct area to be irradiated on the basis of CT findings. We used CT scanning as the major means for diagnosis of tumor extent and for follow-up of NPC during and after radiotherapy. This method usually facilitates assessment of the degree and extent of bone destruction. But because of complicated bony structures, CT scanning does

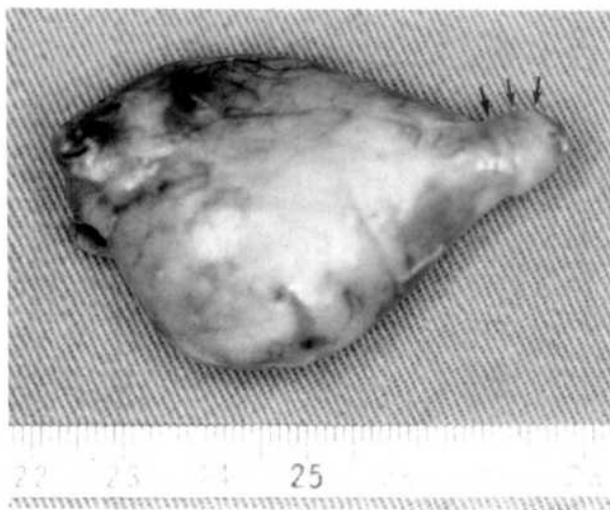


Fig 8. (Patient 7) Macroscopic picture of totally removed tumor. Scale is in centimeters. Arrows — portion located in jugular foramen.

TABLE 2. OUTCOMES OF FIVE PATIENTS WITH NASOPHARYNGEAL CARCINOMA

Patient	Outcome
1	Dead after 4 years owing to multiple metastases to liver and bone
2	No evidence of disease for 68 months
3	Dead after 6 months owing to multiple metastases to bone
4	No evidence of disease for 50 months
5	Alive with multiple metastases to lungs after 2 years

not always provide useful information on skull base lesions. For this, MRI is superior to CT scanning, since data on soft tissue extension to the skull base can be obtained. Angiography in combination with digital subtraction shows the relation of the neoplasm to the great vessels.

The nasopharynx and upper part of the parapharyngeal space close to the skull base are relatively inaccessible without major postoperative complications. Access to the nasopharynx is possible through the palate or maxillary sinus. However, operative fields obtained by these routes are too limited and narrow to remove extensive tumors. In 1966, Ross and Sukis⁶ first reported a "pterygoid route" to remove adenoid cystic carcinoma of the nasopharynx. Nessel and Mundnich⁷ described a similar technique in 1974 as "transpterygoid access" or "lateral nasopharyngostomy." We first applied this technique to patient 1 on February 5, 1985. Our experience with four patients with NPC was published in 1988⁸ and prompted us to apply the technique to remove extensive benign neoplasms in the nasopharynx, parapharyngeal space, and skull base. Since then, three more patients, two of whom had benign tumors, have been added to the series. A transmandibular transpterygoid approach offers a wide operative field, making it possible to easily manage large blood vessels and cranial nerves. In addition, the operative field is very close to the surgeon's hands compared to transpalatal, transmaxillary, or other approaches.^{9,10} As Friedman et al¹¹ and Attia et al¹² reported, temporary removal of the ascending ramus of the mandible facilitates obtaining a wider operative field of the skull base. As indicated in the case of patient 5, other approaches may be combined with this transmandibular transpterygoid approach, depending on the location and extent of the lesion.

Fisch⁹ reported the infratemporal fossa approach for recurrent NPCs. His method always leads to loss of hearing ability and involves difficulty in dissecting the medial and inferior surfaces of the neoplasm by direct vision. The distance to the operative field is not short by this route. His group also applied the infratemporal fossa approach for the removal of schwannomas in the jugular foramen.¹³ All seven cases they reported had advanced lesions rated as C2 or C3, indicating tumor involvement of the internal carotid artery above the carotid foramen.

TABLE 3. INTRAOPERATIVE BLOOD LOSS AND POSTOPERATIVE SEQUELAE

Patient	Blood Loss (mL)	Sequelae
1	500	Paresis of soft palate
2	550	None
3	1,070	None
4	850	Infection of mandible
5	500	None
6	550	Paresis of soft palate
7	100	Recurrent laryngeal nerve palsy

The lesion of patient 7 in our report was rated as C1 on the basis of their staging; a transmandibular transpterygoid approach provided sufficient exposure of the tumor and great vessels. Thus, a lesion that does not involve the internal carotid artery above the carotid foramen can be managed by the transmandibular transpterygoid approach. Krespi¹⁰ used a transcervical approach via a midline mandibulotomy to the skull base. He stressed the ease with which a lesion situated very close to the great vessels could be managed. But his approach may not be close to the operative field in some cases. The present method provides a relatively closer route to the operative field in which hearing ability can be completely preserved. In addition, surgeons do not have to worry about postoperative weakness or palsy of the facial nerve. Thus, the present approach offers one practical surgical route to these relatively inaccessible areas.

After removing the large tumor, a remnant of the pterygoid muscles, sternocleidomastoid muscle, or other musculocutaneous flap was moved into the operative field for the purpose of protecting the great vessels and filling the resulting dead space. A small defect in the mucous membrane of the nasopharynx does not have to be covered as long as the great vessels are secured against bacterial infection. Patient 4 suffered from postoperative infection of the mandible. After conservative treatment of a few months' duration, the infected parts of the mandi-



Fig 9. (Patient 7) Postoperative facial view, showing trismus measurement.

ble and miniplate were removed and the wound rapidly healed, leaving slight difficulty in opening the mouth. Hyperreactivity of the skin, mucous membrane, and other soft tissues to irradiation was strongly suspected as the main cause of the infection. For this reason, a sufficiently long period (4 to 5 weeks) between radiotherapy and surgical therapy is necessary.

Of five patients with failed irradiation as the primary treatment for NPC, two have been alive with no evidence of disease for 68 months and 50 months, respectively, while two died of multiple metastases to the liver and/or bones 4 years and 6

months after treatment, respectively. Patient 5 is alive with distant metastases in the lungs. These results suggest that operative intervention for cases of irradiation failure might be useful, provided the residual tumor is resectable. Since the number of NPC cases in the present series is small, the usefulness of surgical removal of the postirradiation residual NPC is not clear.

In conclusion, our experience with the present series proved that the transmandibular transpterygoid approach is a useful surgical route in the treatment of neoplastic lesions in the nasopharynx, parapharyngeal space, and skull base.

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HEARING LOSS AS A SEQUEL OF LUMBAR PUNCTURE

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Only a few case reports have been published about hearing impairment following lumbar puncture, and not all were thoroughly documented by audiograms. We present nine cases of hearing loss following myelography, lumbar puncture, and spinal anesthesia. We speculate that this rare complication arises only in persons with a wholly or partially patent cochlear aqueduct, and occurs via the release of perilymphatic fluid in the cerebrospinal space. Hearing loss was seen in eight of the nine patients in the lower frequencies, and in six of the nine patients on both sides. Recovery to normal hearing was noticed in six of the nine patients. Transient hearing loss may occur more often than it is generally assumed, and the symptom can remain unnoticed. Since not all of these hearing losses proved to be fully reversible, we suggest informing patients about this complication for medicolegal reasons.

KEY WORDS — complications, hearing loss, lumbar puncture, myelography, spinal anesthesia.

INTRODUCTION

Lumbar puncture, which patients undergo for myelography, spinal anesthesia, and aspiration of cerebrospinal fluid (CSF), is a very common procedure. Sequelae like headache and dizziness following the procedure are well recognized but also rare complications involving cranial nerves, eg, oculomotor, trochlear, abducens, and facial nerves.

In a few case reports hearing loss following lumbar puncture has been described, although the first publication concerning this complication dates from 1914.¹ In neither current textbooks of neurology or neurosurgery nor review articles is this complication mentioned. Only in the textbook of Collins² did we find mention of an incidence (about 2 per 1,000).

Reviewing the few articles concerning hearing loss after lumbar puncture, myelography, and spinal anesthesia, we found no uniform explanation. Authors assumed side effects of contrast media, concomitant ischemic episodes, or an open cochlear aqueduct to be the cause of the hearing loss.

In recent years, we observed nine patients with acute unilateral or bilateral hearing loss following the above-mentioned interventions (see Table). No patient presented a history of previous inner ear dis-

eases, and all assured us that they had normal hearing before the puncture.

CASE REPORTS

Case 1. A 34-year-old man underwent myelography with iopamidol on June 1, 1987. Two or 3 hours after the intervention he complained of headache, nausea, and vertigo. A short time later he noticed a decrease in hearing sensitivity of his left ear. The pure tone audiogram indicated a 30-dB sensorineural hearing loss in the low frequencies. In the next few days the hearing loss improved. On June 25, 1986, a normal audiogram was obtained. Vestibular function seemed to be normal in the diagnostic procedures used, including caloric testing.

Case 2. A 42-year-old woman was presented by a neurologist on February 24, 1987. She reported a bilateral hearing loss and tinnitus that had immediately followed myelography on February 19, 1987. Findings on otologic examination were unremarkable. The pure tone audiogram documented a bilateral hearing loss in the low frequencies of about 70 dB. The stapedius reflex could be elicited on both sides. Therapy with infusions was immediately started and in the following weeks the hearing increased slowly to a bilateral hearing loss of about 20 to 30 dB (Fig 1). In all supplemental tests no lesion of the eighth nerve could be found.

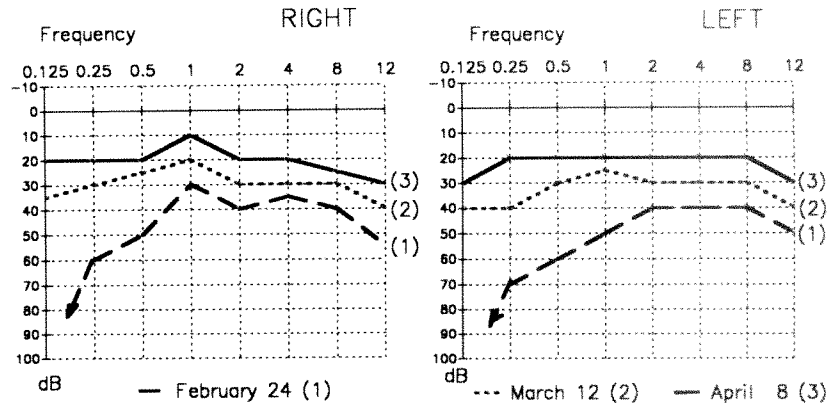
AGE, SEX, TYPE OF INTERVENTION, FREQUENCIES, MAXIMUM HEARING LOSS, SIDE AFFECTED, AND RESULT AFTER THERAPY

Case	Age	Sex	Intervention	Frequency	Side Affected	Hearing Loss	Recovery
1	34	M	Myelography	Low	Unilateral	30 dB	Complete
2	42	F	Myelography	Low	Bilateral	70 dB	Partial
3	44	M	Spinal anesthesia	High	Bilateral	40 dB	None
4	31	M	Myelography	Low	Unilateral	40 dB	Complete
5	42	F	Spinal anesthesia	Low	Bilateral	30 dB	Complete
6	45	M	Lumbar puncture	Low	Bilateral	40 dB	Complete
7	54	M	Myelography	Low	Bilateral	30 dB	Complete
8	53	M	Spinal anesthesia	Low	Bilateral	30 dB	Complete
9	61	F	Lumbar puncture	Low	Unilateral	60 dB	None

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REPRINTS — Olaf Michel, MD, ENT Dept, University of Cologne, Joseph-Stelzmann Strasse 9, D-5000, Cologne, Germany.

Fig 1. (Case 2) Audiograms taken February 24 (1), March 12 (2), and April 8 (3), 1987, showing hearing loss following myelography performed on February 19. There was partial bilateral recovery to hearing levels of 20 to 30 dB.



Case 3. The third case involved a 44-year-old man who underwent spinal anesthesia for the removal of a metal splint in his right leg. Immediately after the uncomplicated intervention he felt fullness in his ears, severe headache, and vertigo, later associated with vomiting. He also complained about a bilateral hearing loss. The consulting otolaryngologist observed a spontaneous nystagmus directed to the left that lasted for 5 days. At a later date, nevertheless, the caloric testing proved normal sensitivity of both labyrinths. Maskable at 6 to 8 kHz with 45 dB, the initial tinnitus remained unchanged. Also, the hearing loss did not improve in spite of treatment. The pure tone audiogram showed a 40-dB hearing loss at 4 to 6 kHz. A lesion of the eighth nerve was excluded.

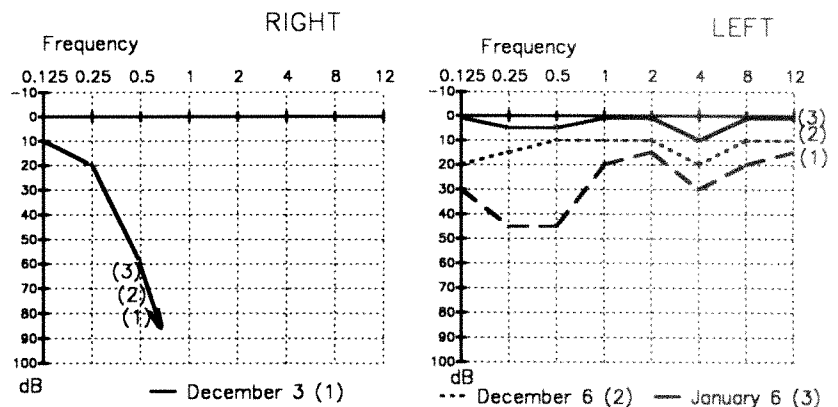
Case 4. Shortly after lumbar myelography on November 25, 1982, a 31-year-old man felt a strong headache combined with pain in the neck and nausea. On December 3, 1982, he noticed a hearing loss in his left ear that led him to consult an otologist. Findings on examination were unremarkable. Since he had been 13 years old he had had a hearing loss of unknown cause in his right ear. The pure tone audiogram of December 3, 1982, revealed in the left ear a sensorineural hearing loss both in the low frequencies (45 dB) and in the high frequencies (30 dB). In the right ear a downward slope was noted with deafness in the frequencies above 1,000 Hz. The hearing did not improve on the left side, and therefore an exploratory tympanotomy was performed while taking into consideration that it was

the only hearing ear of this patient. The inspection of both windows did not show any perilymphatic fistula. Postoperatively the hearing improved under infusions with pentoxifylline and low-molecular weight dextran. On January 6, 1983, a pure tone test showed a normal hearing level on the left side with a small depression of 21 dB at 4 kHz and an unchanged level on the right side (Fig 2).

Case 5. On October 22, 1987, 1 day after the removal of a prevesicular stone in the left ureter under spinal anesthesia, a 42-year-old woman was struck by a strong headache and subsequent vertigo with vomiting. On the second postoperative day the patient noticed a bilateral decrease of hearing, predominantly in the left ear. Additionally, she had tinnitus, perceived as a deep roaring sound. An otolaryngologic examination revealed no pathologic findings. The pure tone audiogram showed a hearing loss of about 30 dB on the right and 40 dB on the left, situated particularly in the low frequencies. Therapy was started immediately with hemorrhheologically effective infusions. Hearing recovered to normal and the tinnitus entirely disappeared within 7 days.

Case 6. On July 15, 1988, a 45-year-old patient underwent a lumbar puncture. Within the first 24 hours the patient complained of a headache that intensified in the upright position. The second day after the puncture the patient felt fullness and a roaring sound in both ears. For a short period vertigo also was present. The first pure tone audiogram was

Fig 2. (Case 4) Audiograms taken December 3 (1) (8 days after lumbar myelography) and December 6 (2), 1982, and January 6 (3), 1983. There was nearly complete recovery in left ear.



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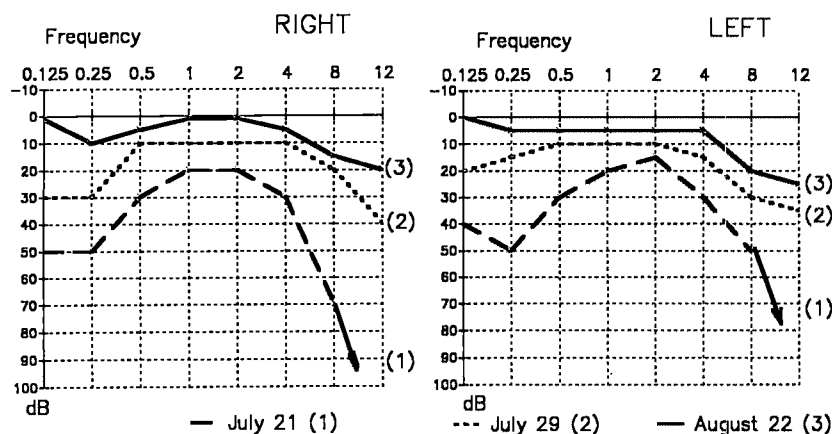


Fig 3. (Case 6) Hearing loss after lumbar puncture on July 15, 1988. First audiogram was taken July 21 (1). Second audiogram was taken July 29 (2). There was complete recovery by August 22 (3).

performed July 21, indicating a bilateral deterioration of hearing of about 40 dB in the low frequencies and a high-tone slope (Fig 3). Results of caloric testing were normal. Therapy was started immediately and within 4 weeks the hearing loss was restored to normal levels.

Case 7. To exclude a prolapse of an intervertebral disk, a 54-year-old patient underwent myelography on August 28, 1988. On the evening of the same day he developed a strong headache. The morning after he noted a bilateral hearing deterioration without vertigo or tinnitus. The pure tone audiogram (August 30, 1988) suggested a bilateral sensorineural deafness of about 30 dB in the low frequencies and a high-tone slope of 70 dB. Under therapy with infusions consisting of low-molecular weight dextran, cortisone, and pentoxifyllin, the hearing loss recovered completely.

Case 8. The second day following a meniscus operation under spinal anesthesia a 53-year-old patient noticed a hearing loss predominantly in the left ear, slight tinnitus, and vertigo. The pure tone audiogram revealed a bilateral low-frequency depression of about 20 to 30 dB. In the higher frequencies there was a known noise-induced hearing loss about 60 to 70 dB. The low-frequency hearing loss recovered to normal levels under immediately initiated therapy with infusions.

Case 9. One day after a diagnostic lumbar puncture, a 61-year-old woman complained about left-sided hearing deterioration. An audiogram was carried out and revealed a hearing loss of about 60 dB in the low frequencies with an up-slope to 30 dB at 2 kHz and normal hearing in the right ear. Additionally, a spontaneous nystagmus could be seen directed to the left side. Three days later this nystagmus had disappeared, and caloric testing reflected a normal response of both labyrinths. In spite of promptly initiated therapy, the hearing loss did not recover.

DISCUSSION

After lumbar myelography, transient hearing loss has been described and ascribed to the side effects of contrast media such as metrizamide³ and iohexol or

iopamidol.⁴ The authors suggested that these water-soluble contrast agents might produce a hydrostatic imbalance between perilymph and CSF due to a decrease in CSF osmolality. Also, an indirect action of the contrast media via systemic absorption has been suggested. Neither pathogenetic theory seems to be likely, because on the one hand contrast agents have been applied successfully in the treatment of sudden hearing loss,⁵ and on the other hand, not very much of the agent will pass the blood-CSF barrier.

In 1977 a case report was published by Loers⁶ about a reversible unilateral low-frequency hearing loss following spinal anesthesia. Panning and Lehnhardt⁷ noted this report and examined the hearing of 100 consecutive patients undergoing spinal anesthesia. In three cases a hearing loss in the low-frequency range could be detected after the intervention. They explained their findings as endolymphatic hydrops due to the loss of CSF during the procedure, and postulated the resulting hypotension in the cerebrospinal space in terms of a relatively wide cochlear aqueduct.

A higher incidence of hearing loss has been reported by Wang et al,⁸ who saw transient hearing disturbance under spinal anesthesia in 6 of 14 patients.

The hypothesis of an open cochlear aqueduct must be kept in mind when we include the observations of altered hearing following lumbar puncture in which no drugs were applied. In 1961 three cases of hearing loss were the topic of a thesis.⁹ In 1963 the otologist Arnvig¹⁰ described his own history of a transitory decrease in hearing after lumbar puncture and also speculated about the possible role of the cochlear aqueduct in this phenomenon. This theory would be congruent with the 1988 report of Hardy,¹¹ who saw two patients with continuing loss of hearing after spinal puncture. He restored the auditory disturbance by injection of 20 mL of isotonic sodium chloride into the subarachnoid space.

A hydrodynamic relationship between the CSF and the perilymph fluid might exist via the cochlear aqueduct (Fig 4). The cochlear aqueduct connects the subarachnoid space and the perilymphatic space.

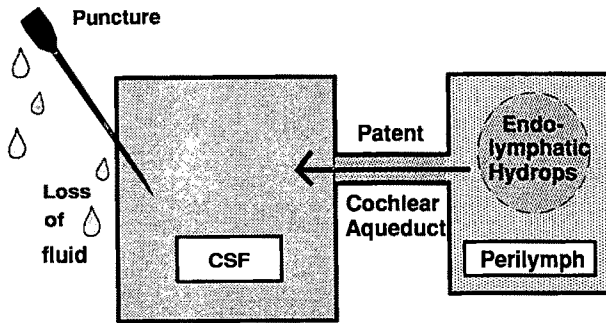


Fig 4. Schematic drawing of possible underlying pathologic mechanism of hearing loss under assumption of patent cochlear aqueduct. CSF — cerebrospinal fluid.

Its diameter varies between 0.1 and 0.2 mm and its length is about 6.2 mm.¹² It extends from the posterior fossa roughly parallel to the internal auditory meatus to the scala tympani near the round window membrane. In adults a loose meshwork containing collagen and elastin fibrils obstructs its lumen so that any flow must be very slow. Its physiologic significance is not yet clear; the possibilities of filtration function or simply a damper function to reduce sudden pressure variations occurring between the perilymph and the CSF were discussed.^{13,14}

Histologically, in larger human temporal bone studies unilateral closed or absent cochlear aqueducts were noted,¹⁵ as well as wide open cochlear aqueducts in children.¹⁶

An open or insufficiently closed cochlear aqueduct is also thought to be present when an "oozer" occurs during a stapes operation.¹⁴ Since the flow rate in the cochlear aqueduct depends on its diameter and is therefore limited, the more dramatic "gushers" with their rapid flow must depend on larger shunts between the perilymphatic and cerebrospinal spaces.¹³ This phenomenon will be seen in about 1 to 2 per 1,000 of all operations with fenestration or removal of the footplate. Thus, the incidence of this complication falls within the estimated rate of hearing loss following lumbar puncture,² in which an open cochlear aqueduct is also thought to be the underlying pathologic substrate.

Indeed, under the assumption of an open or only partly closed cochlear aqueduct, the loss of CSF during or after the puncture could nonetheless

cause a loss of perilymphatic fluid. The lowering of perilymphatic pressure relative to the endolymphatic pressure would lead to an endolymphatic hydrops and a resultant displacement of the basement membrane. This assumption would explain the fact that the hearing loss is mostly low-frequency, the sometimes unilateral occurrence, and the high rate of recovery.

The individual risk of post-spinal puncture hearing loss is not predictable in the absence of any criteria. In high-resolution computed tomography the aqueduct is hard to delineate and its internal soft tissue anatomy is impossible to determine.

In comparison to the large number of lumbar punctures besides those in connection with spinal anesthesia and myelography, reports about hearing disorders are extremely rare, since normally the damper function of the fibrils within the aqueduct prevents a loss of perilymphatic fluid into the cerebrospinal space. The leakage through the dural puncture may cause a loss of up to 20 mL of CSF. In such a case of a severe post-spinal puncture syndrome with headache, dizziness, and nausea the additional symptom of hearing loss may easily be overlooked, especially when the other symptoms dominate the discomfort of the patient. As the majority of these interventions lie in the hands of neurologists, neurosurgeons, or anesthesiologists, an otologist may be informed too late. In the great majority of these cases the hearing loss recovers spontaneously, so that later there seems to be no need for a hearing test.

In a case of affected hearing, spontaneous recovery should not be expected and treatment by intravenous infusions should be started immediately. To stop the leakage of CSF, epidural blood patching could be tried additionally. In order to replace the fluid loss one may inject isotonic sodium chloride through the catheter into the subarachnoid space.

Three of our nine patients complained of a lasting auditory distortion and two of them instituted malpractice proceedings against their treating physicians. Therefore, we recommend informing the patient before the intervention about a possible lasting hearing loss, even though the incidence is low.

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EFFECT OF THE RADIOPROTECTOR WR2721 ON IRRADIATION-INDUCED INJURY TO CILIATED CELLS OF EUSTACHIAN TUBE

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Our previous studies revealed that injury to the ciliated cells of the eustachian tube may be the primary cause of irradiation-induced serous otitis media. The purpose of this study was to investigate the effects of the radioprotector WR2721 on irradiation-induced injury to ciliated cells of the eustachian tube (ET) in chinchillas. Twelve chinchillas were divided into two groups: the control group and the experimental group, which was pretreated with a single intraperitoneal dose of the radioprotector S-2-[3-aminopropylamino]ethylphosphorothioic acid (WR2721) 400 mg/kg. The two groups were exposed to 30 Gy of 13-MeV electrons in a single fraction to the area of the bullae and nasopharynx. Ciliary dysfunction was tested and ciliated cells of the ET were examined by scanning and transmission electron microscopy. Pretreatment with WR2721 was found to protect ciliated cells of the ET from irradiation injury.

KEY WORDS — ciliated cells of eustachian tube, eustachian tube function, radiation-induced otitis media, radiation injury, radioprotector WR2721.

INTRODUCTION

Radiotherapy is a valuable treatment modality in the management of patients with head and neck tumors. One of the common findings after radiotherapy is, however, serous otitis media (SOM).¹ O'Neill et al² reviewed 14 cases of patients treated with irradiation for nasopharyngeal malignancies and found 7 patients with SOM. Gamble et al³ studied the effects of irradiation on the ear and observed that the most immediate problem encountered was SOM secondary to inflammation of the middle ear (ME) and eustachian tube (ET).

The lining of the ME and ET is similar to other respiratory mucosa in that it has a mucociliary system composed of ciliated cells, secretory cells, and a mucous blanket.⁴⁻⁶ Irradiation damages the ciliary motility, leading to delayed clearance of exudate and secretions and thus resulting in otitis media with effusion.^{7,8} Clearance of the ME is an active process and a result of ciliary function as well as muscular action.^{9,10} We hypothesized that the mucociliary dysfunction of the ET may be the primary cause of irradiation-induced otitis media.

Chemical modification of irradiation response has received renewed interest over the last two decades as a possible adjunct to irradiation in the treatment of cancer. Gamble et al³ suggested the possibility of

using a drug that would modify the negative effects of irradiation and potentiate the effects of irradiation in the treatment of cancer. Chemical radiation modifiers have been evaluated to protect normal tissue with minimal effects on the radiosensitivity of malignant tissue.^{11,12} This allows for increased doses of radiation to be given to tumor tissue.^{13,14}

One of the most effective radioprotectors available is S-2-[3-aminopropylamino]ethylphosphorothioic acid (WR2721).¹⁵⁻¹⁸ In a comparison study of the protective effects of several phosphorothioates, WR2721 was shown to be the most effective radioprotector on a molar basis.¹⁹ Survival increased in irradiated animals pretreated with WR2721.¹⁶ A variety of organ systems have been protected from radiation injury with pretreatment with WR2721.^{18,20,21} It has been shown to preferentially protect normal tissue as compared to malignant tissue of tumor-bearing laboratory animals from radiation injury.^{21,22} A major factor for this difference is that WR2721 is concentrated by normal tissues but is passively absorbed by solid tumors.²³ Studies with mice have shown WR2721 to protect against irradiation-induced pneumonitis, including late pulmonary fibrosis,²⁴ and also irradiation-induced nephropathy.²⁵ Yuhas²³ has reported a 1.6-fold increase in the resistance of head and neck cancer patients to irradiation-induced stomatitis with pretreatment of WR2721.

From the Division of Otolaryngology-Head and Neck Surgery, Department of Surgery (Panossian, Jung, Park, Miller), the Department of Pathology (Weeks), and the Division of Radiation Oncology, Department of Radiology (Sandefur), Loma Linda University School of Medicine, Loma Linda, California, and the Departments of Radiology and Radiation Oncology, University of Washington, Seattle, Washington (Krohn). Supported by a research grant from the Deafness Research Foundation (T.T.K.J.). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Jerry L. Pettis Veterans Hospital, Loma Linda, California.

Presented at the meeting of the American Academy of Otolaryngology-Head and Neck Surgery, New Orleans, Louisiana, September 21-23, 1989.

REPRINTS — Timothy T. K. Jung, MD, PhD, Inland Ear, Head & Neck Clinic, 3975 Jackson St, Suite 202, Riverside, CA 92503.

Ohashi et al⁸ irradiated guinea pigs with a single dose of 30 Gy of x-rays and found serous effusion in each tympanic cavity of all the animals. Pathologic abnormalities were similar to those of human serous otitis media, including degeneration of the cilia or ciliated cells and changes in the vascular system.

The purpose of the present study was to investigate the effect of the radioprotector WR2721 on irradiation-induced injury to ciliated cells of the ET in chinchillas. The results of this study will be useful clinically to minimize irradiation injury to the ME and ET for patients receiving radiotherapy for head and neck malignancies.

MATERIALS AND METHODS

Animals. Twelve healthy chinchillas weighing approximately 500 g without evidence of otologic or upper respiratory tract infection were used for this study. Six of the animals were controls, while the remaining six were pretreated with WR2721. The chinchillas were chosen as the experimental animal because they are relatively resistant to upper respiratory tract and ME infections and they have large and accessible bullae.

Radiation Treatment. The two groups of animals were exposed to 30 Gy (4 Gy/min) in a single fraction using 13-MeV electrons to the area of the nasopharynx and bullae. The rest of the body of the chinchillas was protected by a lead blanket. To eliminate the need for anesthesia during the treatment, a holding device was used that was made from 7.5-cm polyvinyl chloride pipe with a cutout allowing the head to be exposed.²⁶

Experimental Protocol. Six animals were pretreated with WR2721 dissolved in sterile distilled water (40 mg/mL) immediately before injection. A single intraperitoneal injection (400 mg/kg)²⁷ was given 45 minutes prior to irradiation. Six control animals received a single intraperitoneal injection of the same volume of sterile distilled water 45 minutes prior to irradiation. At 1 and 2 weeks postirradiation, two control and two WR2721-treated animals were painlessly killed. All animals underwent otoscopy and tympanometry under ketamine hydrochloride anesthesia (30 mg/kg intramuscularly) before being killed.

Measurement of Mucociliary Clearance. Animals underwent evaluation of the ET mucociliary function before being killed. A simple measurement of the rate of dye transport through the ET was used as described by Bakaletz et al.²⁸ The soft palate of the anesthetized chinchillas was split open to allow visualization of the ET orifice in the nasopharynx. Then 0.5 mL of 5% Coomassie brilliant blue solution was injected into the superior bullae and allowed to travel to the nasopharynx, where its appearance was monitored with an operating micro-

scope. The time elapsed from the injection of the dye to the appearance in the nasopharyngeal orifice of the ET was measured.

Dissection of Middle Ear and Eustachian Tube. Under deep anesthesia, all animals were perfused with fixatives through a catheter in the aorta inserted through the left ventricle of the heart. The animals designated for temporal bone histopathology were perfused with buffered 10% formalin. The animals designated for transmission electron microscopy (TEM) and scanning electron microscopy (SEM) were perfused with 2.5% glutaraldehyde. After adequate perfusion, the entire skull and nasopharynx were dissected out for temporal bone histopathology and TEM and SEM of the epithelial cells of the ET.

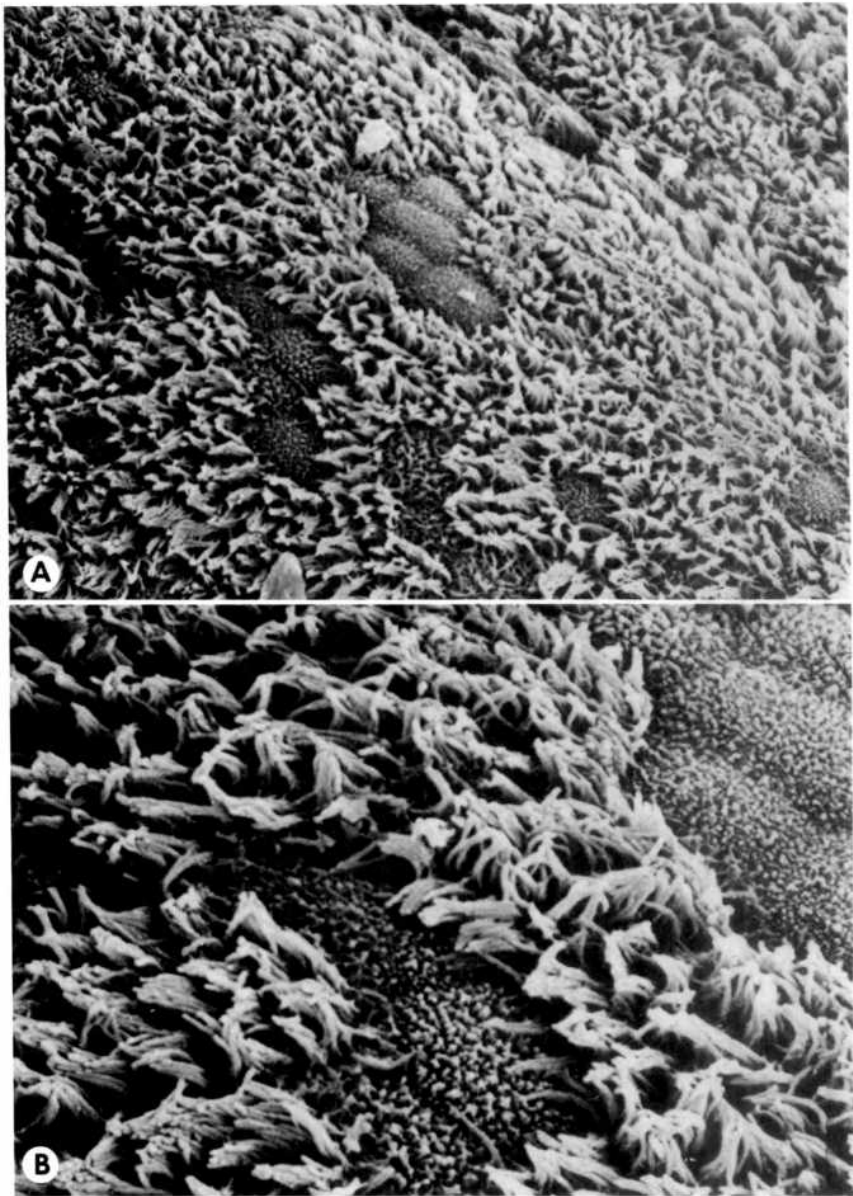
Scanning Electron Microscopy. The ETs were dissected out from both sides of the skull specimens by using an operating microscope. The entire ET was longitudinally opened and sutured open at four points on a cut piece of cardboard. Specimens were quickly placed in 2.5% glutaraldehyde with a 0.1 mol/L phosphate buffer. The specimens were rinsed in 0.1 mol/L cacodylate buffer pH 7.12. A mucolytic agent, 2% *N*-acetyl-L-cysteine in 0.01 mol/L cacodylate buffer solution, was used to remove the mucous blanket. The ET specimens were then post-fixed in 1% osmium tetroxide and then rinsed in cacodylate buffer. The specimens were dehydrated in a series of acetone solutions. Then the specimens were critical point dried with carbon dioxide, gold coated, and viewed with an AMR model 1000 scanning electron microscope.

The ciliary morphology of controls was compared with that of the radioprotected group in terms of abnormal branching, disorientation, and observable numeric decreases in cilia.

Transmission Electron Microscopy. The sample was dissected in a similar manner as for the SEM and sutured open on a cut piece of cardboard. The samples were fixed in 2.5% glutaraldehyde, washed in 0.1 mol/L cacodylate buffer pH 7.12, and post-fixed in 1% osmium tetroxide. The specimen was stained en bloc with uranyl acetate saturated in 10% acetone. The sample was dehydrated in a series of increasing concentrations of acetone and embedded in Epon. Thick sections of 1 μ m were made and stained with toluidine blue, and proper areas of sectioning were selected. Thin sections of the selected area were grid-stained with uranyl acetate saturated in 10% acetone and lead citrate. Specimens were viewed on a Philips EM 400 transmission electron microscope.

Ultrastructural features of tissue from control and radioprotected animals were compared with each other and with comparable tissue from normal animals.

Fig 1. Scanning electron photomicrographs of eustachian tubes of 2-week controls. A) Increase in nonciliated cells with increased ciliary clumping and tangling (original $\times 1,700$). B) Original $\times 4,250$.



RESULTS

All animals were followed up for 2 weeks. Two animals each from the control and experimental groups were killed painlessly at 1 and 2 weeks, and ETs were examined by SEM and TEM. Some of the animals did poorly 1 week after radiation exposure. Animals that were doing poorly were killed first. On the 11th day postirradiation, from the experimental group, one animal died and two were killed because of impending death. On the 13th day postirradiation, one animal each from the control and experimental groups died.

Otoscopic examination at 7 days of the control animals showed moderately inflamed external auditory canals and normal-appearing tympanic membranes without evidence of effusion. Otoscopy of experimental animals showed mildly inflamed external auditory canals with normal tympanic membranes. There was no change in otoscopic findings

after 2 weeks from irradiation in both control and experimental animals.

Tympanometry at 7 days postirradiation revealed 11 of 12 ears with type A tympanograms, and 1 of 12 ears from the experimental group with type B. After 2 weeks, tympanometry of the 6 control ears demonstrated 2 with type A, 2 with type B, and 2 with type C tympanograms.

Dye transport times for controls at 1 week were 885.8 ± 44.4 seconds ($n = 4$), and 2 weeks postirradiation they were greater than 960.0 seconds ($n = 2$), which is more than four times normal (217 seconds)²⁶ for our laboratory. The experimental group dye transit times at 1 week were 87.5 ± 70.0 seconds ($n = 4$) and at 2 weeks 630.0 ± 339.4 seconds ($n = 2$). Statistical significance was not calculated because of the small sample size. No data were collected on one of the 2-week controls because of severe bleeding.

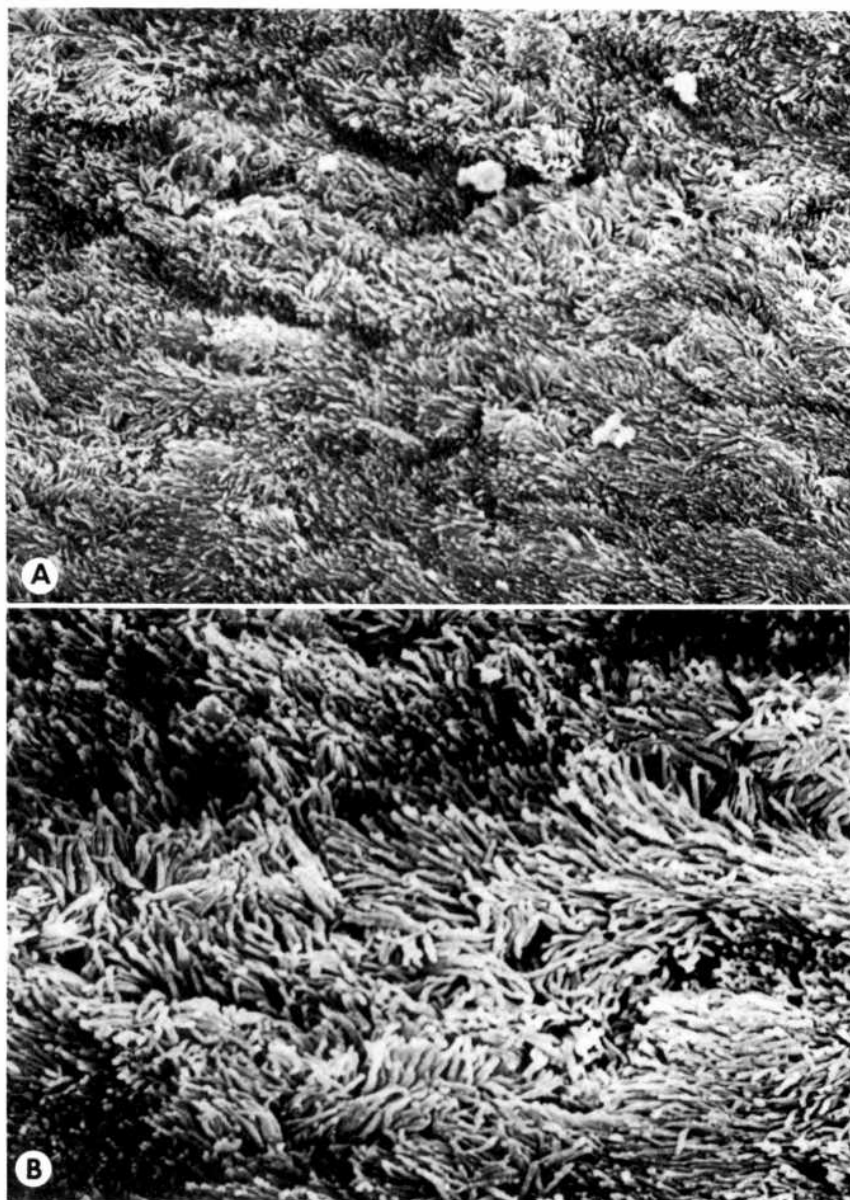


Fig 2. Scanning electron photomicrographs of eustachian tubes of 2-week WR2721-pretreated chinchillas. A) Normal fields of ciliated cells (original $\times 1,760$). B) Normal intact cilia are present (original $\times 4,400$).

In our experience the use of 0.15 mL of Coomassie blue dye solution resulted in dye transit times of greater than 30 minutes, which were much longer than those of Bakaletz et al.²⁸ We used increments of 0.1 mL of dye solution injected with a venting needle in place until the dye transit times consistently were less than 15 minutes. Our end point was the first sign of definite blue color seen at the nasopharyngeal orifice of the ET with an operating microscope. A volume of 0.5 mL was found to give consistent and reproducible results. A different end point used and laboratory variability may account for the differences in the volume of dye solution that had to be used in our laboratory.

The SEM of the ETs from the control group at 1 week showed mild clumping and tangling of cilia. At 2 weeks the ET from the control group showed more clumping and increased tangling of cilia with an increase in nonciliated cells (Fig 1). The SEM of

the ETs from the experimental group pretreated with WR2721 revealed essentially normal cilia at both 1 and 2 weeks (Fig 2).

The TEM of the ETs from the control group at 1 week demonstrated moderately disorganized ciliated cells as compared with comparable tissue from normal animals. This included increased variation in cell outlines, nuclear placement and shape, and cell stratification. There was also cytoplasmic edema, mild swelling, and upward displacement of goblet cells (Fig 3A). At 2 weeks, TEM of the ET from the control group demonstrated areas of severe cellular disorganization, mosaiclike ciliated epithelium, severe vacuolization, areas of autophagocytosis, loss of nuclear polarity, increased cellular rounding with swelling of the organelles, degeneration of goblet cells, and increased numbers of nonciliated epithelial cells (Fig 3B,C). The cilia remained intact at both 1 and 2 weeks.

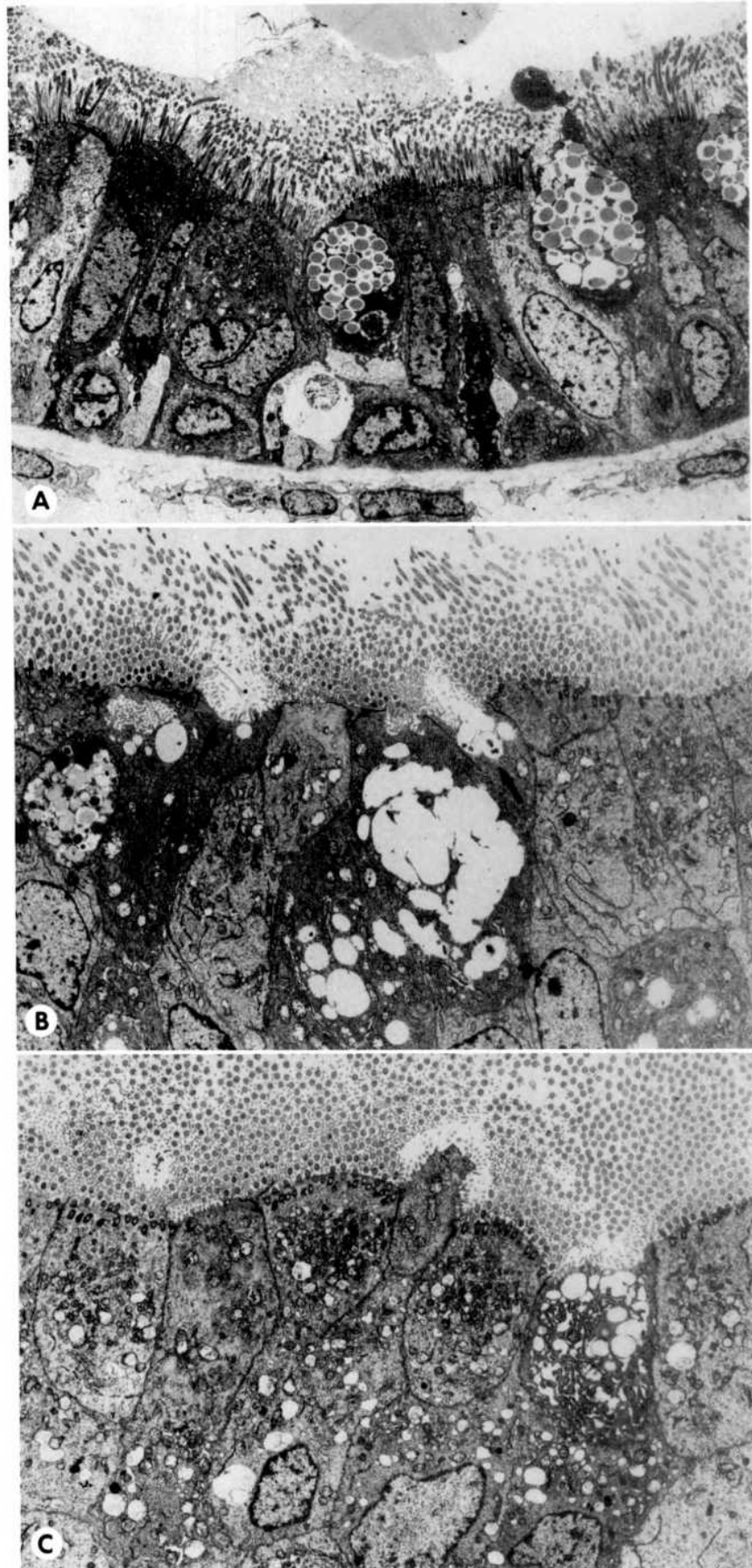


Fig 3. Transmission electron micrographs of eustachian tubes of control animals. A) At 1 week (original x3,000). Moderately disorganized ciliated cells with mild vacuolization, moderate loss of nuclear polarity, and mild intercellular space expansion. Goblet cells are swollen and displaced toward surface. B) At 2 weeks (original x5,000). Severely disorganized, mosaiclike ciliated epithelium with intracytoplasmic edema. Surface depression and irregularities are noted (arrows). Cilia are intact without swelling. C) At 2 weeks (original x4,400). Severely disorganized ciliated epithelium with conspicuous vacuolization and loss of nuclear polarity. Autophagocytosis, increased cellular rounding with swelling of organelles, degenerating goblet cells, and increased number of nonciliated epithelial cells are seen.

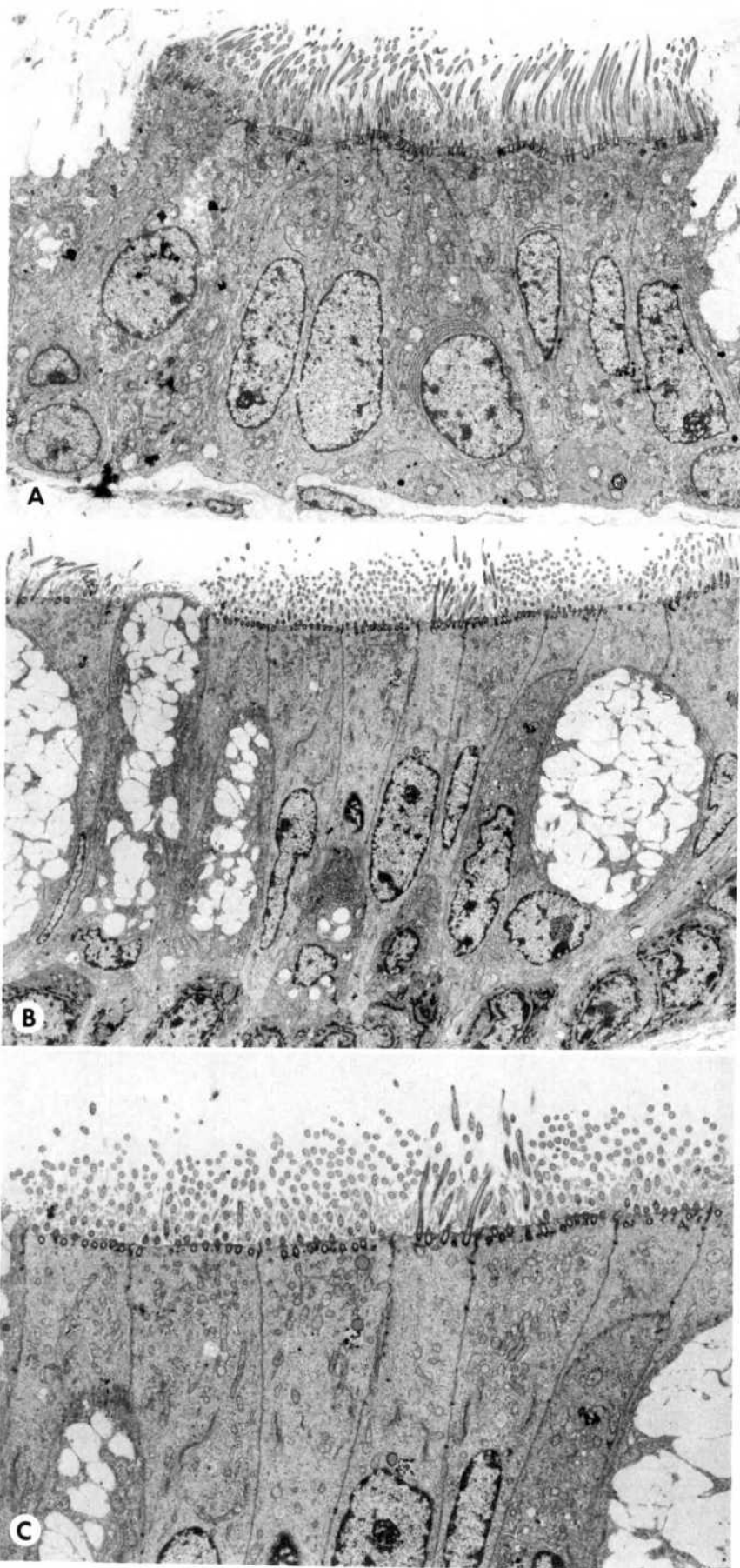


Fig 4. Transmission electron micrographs of eustachian tubes of WR2721-pretreated animals. A) At 1 week (original x1,500). Cellular organization is intact with minimal vacuolization and mild loss of nuclear polarity. Cilia are intact. B) At 2 weeks (original x2,500). Cellular organization remains intact with only mild loss of nuclear polarity. C) At 2 weeks (original x5,300). Cilia and cellular organization are intact. Apical surfaces are smooth.

The TEM of the ETs from the WR2721-pretreated group at 1 week exhibited nearly intact cellular organization and mild vacuolization (Fig 4A). At 2 weeks, the TEM of the ETs from the experimental group demonstrated intact cellular organization, mild loss of nuclear polarity, well-preserved goblet cells, and minimal cellular swelling without autophagocytosis (Fig 4B,C). Cilia remained intact at both 1 and 2 weeks.

DISCUSSION

We attribute the mortality of the animals in this experiment to the high single-fraction dose of 30 Gy radiation to the nasopharynx. Another mechanism that may have caused premature death was behavioral toxicity caused by a combination of irradiation and WR2721.¹⁵ Dehydration secondary to irradiation-induced oral mucositis may have contributed to the premature death.

Otoscopic examination demonstrated no evidence of ME effusion in any of the animals at both 1 and 2 weeks postirradiation. Two thirds of the control animals at 2 weeks had type B or type C tympanograms indicating ET dysfunction. Because of the short life span of these animals following irradiation, they did not develop detectable ME effusion. In our previous study with chinchillas, ME effusion did not become apparent until 2 months postirradiation.²⁶

Increased dye transport times for the control group indicated impaired ciliary motility of the ET

due to irradiation injury. Irradiation injury in control animals was grossly evident by desquamating, friable, and dehydrated oral mucosa. Decreased ciliary motility in guinea pigs after a single fraction of radiation was shown by Ohashi et al.⁸ Dye transport times for the pretreated experimental group at 1 week were similar to those of the normal controls, indicating no change in ciliary motility. At 2 weeks the increased dye transport times of the experimental group may have been due to dehydration.

The SEM and TEM of the ETs consistently demonstrated pathomorphology in the control group, while the ultrastructure of the ETs of the WR2721-pretreated group remained essentially normal. The fact that the radioprotector WR2721 provided protection from irradiation injury to the ciliated cells of the ET in chinchillas indicates that it is taken up by the ET in large enough amounts to protect against irradiation injury.

In conclusion, we have shown that irradiation causes severe injury to the ciliated epithelium of the ET in chinchillas and that pretreatment with WR2721 provides effective protection from irradiation-induced injury to these cells. Clinical application of this finding may include pretreatment with WR2721 applied topically into the ME, which may minimize the toxic effects of WR2721 and inhibit the pathologic changes seen in irradiation-induced otitis media.

ACKNOWLEDGMENTS — The authors thank Mary Metzler for help in preparing the transmission electron microscopy specimens and photographs, Debbie Torbitt for help in preparing the scanning electron microscopy specimens and photographs, Nancy Mitchell for help with the processing of the temporal bones, and Martha Branson and Patti Wilbur for help with the manuscript.

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The UCSF Otolaryngology Update: 1992, will be held November 5-7, 1992, at the Ritz-Carlton Hotel in San Francisco, California. For more information, contact the University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; telephone: (415) 476-4251.



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ELECTROCOCHLEOGRAPHY IN THE PRESENCE AND ABSENCE OF PERILYMPHATIC FISTULA

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The purpose of the present study was to evaluate the effect of an acute perilymphatic fistula on the amplitude ratio (SP/AP) of the summing potential (SP) and action potential (AP). The effect of the acute fistula on AP threshold was also addressed. Electrocochleographic recordings were obtained before and immediately after surgical laceration of the round window membrane in 19 guinea pigs. Stimuli comprised clicks and 2,000-Hz and 8,000-Hz tone bursts, presented initially at 100 dB peak equivalent sound pressure level and in descending 10-dB steps. After fistula induction the SP/AP significantly increased for the click and 8,000-Hz tone burst stimuli but not for the 2,000-Hz tone burst stimuli. No significant change in AP threshold occurred. These findings suggest that the SP/AP may be sensitive to perilymphatic fistula, at least in guinea pigs. The changes in the SP/AP do not appear to be related to changes in threshold.

KEY WORDS — action potential threshold, electrocochleography, perilymphatic fistula, SP/AP amplitude ratio, summing potential.

INTRODUCTION

In recent years, the amplitude ratio (SP/AP) of the summing potential (SP) and action potential (AP) has been reported to be increased in many cases of Meniere's disease.¹⁻⁴ Hypothetically, the SP/AP can be enlarged because Meniere's disease may alter the pressure gradient across the basilar membrane by increasing endolymphatic pressure. In animal experiments, either increasing perilymphatic pressure above the basilar membrane (scala vestibuli) or decreasing pressure below the basilar membrane (scala tympani) increased SP amplitude for high-level stimuli.^{5,6} Because a perilymphatic fistula could reduce perilymphatic volume and cause a similar deflection of the basilar membrane toward the scala tympani, an enlarged SP/AP could be predicted in the presence of perilymphatic fistula.

Staller⁷ reported an increase in the SP/AP in "some patients" with perilymphatic fistula. In 1987, we found the SP/AP to increase after induction of perilymphatic fistula in the round window in 10 guinea pigs (Campbell et al, unpublished observations). In a retrospective study, Arenberg et al⁸ reported an enlarged SP/AP in 52% of 27 patients with surgically confirmed perilymphatic fistulas. They also reported the SP/AP to enlarge and reverse polarity in 12 guinea pigs with induced round window perilymphatic fistulas, but found the effect to be restricted to lower intensity levels. Only click stimuli were employed in the Arenberg et al study. The effect of perilymphatic fistula on auditory threshold was not addressed in the animal study.

The present study examines the effects of induced perilymphatic fistula on the SP/AP in 19 guinea pigs by employing three different stimuli at three intensity levels.

METHODS

Electrocochleographic recordings were obtained from 19 fully anesthetized (ketamine hydrochloride and xylazine hydrochloride) female adult Hartley guinea pigs of 300 g or less. The bulla was opened by a dorsolateral approach. A silver ball electrode (active) was placed on the wall of the middle ear cavity overlying the lateral semicircular canal. This electrode placement avoided contamination of the recordings by perilymph leakage at the round window. Because perilymph is conductive, contact with the electrode must be avoided to prevent alteration of the current pathway. This placement also appeared to provide the clearest recordings of the SP. A needle reference electrode was placed in the neck, and a needle ground electrode in the ipsilateral foot.

Stimuli included 50-microsecond clicks, and 2,000-Hz and 8,000-Hz tone bursts with a 2-millisecond rise-fall time and 4-millisecond plateau. In human studies a 100-microsecond click is generally employed. But given the higher frequency range of hearing in the guinea pig, a 50-microsecond click was employed to provide more high-frequency energy in the signal. Stimuli were transduced through a Koss VX earphone and delivered via a speculum placed in the external auditory meatus. Stimuli

From the Department of Otolaryngology, The University of Iowa Hospitals and Clinics, Iowa City, Iowa (all authors). Work also was performed in the Division of Otolaryngology, Department of Surgery, Southern Illinois University School of Medicine, Springfield, Illinois (Campbell), and at Boys Town National Research Hospital, Omaha, Nebraska (Harker). Supported by National Institutes of Health grant 1-K08-DC-00040. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of The University of Iowa.

REPRINTS — Kathleen C. M. Campbell, PhD, Division of Otolaryngology, SIU School of Medicine, PO Box 19230, 301 N Eighth St, Springfield, IL 62794-9230.

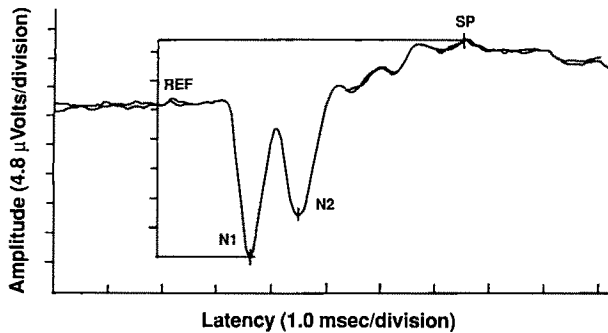


Fig 1. Electrocochleogram demonstrating method of measuring summing potential (SP) amplitude for tone burst stimuli. REF — reference point for measurement.

were presented at 15.7 per second in descending 10-dB steps from 100 dB peak equivalent sound pressure level (peSPL) to 10 dB below observed response. Intensity was then increased in 5-dB increments to determine the lowest level at which replicable AP activity could be observed for each of the three stimuli, and this level was then considered the threshold. Only the intensity levels of 100, 90, and 80 dB peSPL were used for analysis of the SP/AP amplitude ratio to obtain maximal SP clarity for analysis.

Alternating polarity stimuli were used to reduce stimulus artifact and cochlear microphonic activity in the recordings. If monopolarity stimuli are employed, SP and AP measures are confounded by the sinusoidal activity of these two components.

The electrical recording was digitized every 0.02 millisecond over a 2-millisecond period preceding the stimulus and over an 8-millisecond period following the stimulus.

Responses were filtered with a band pass of 5 Hz to 3,000 Hz. Each trial consisted of 250 sweeps per average.

The amplitude of N1, the first peak of the AP, was measured from the prestimulus baseline to the maximal peak of the waveform. For click stimuli, the amplitude of the SP was measured from prestimulus baseline to the peak of the SP waveform preceding N1. For tone bursts, the SP was measured from the prestimulus baseline to a point 5.5 milliseconds after stimulus onset, during the plateau of the stimulus (Fig 1). In humans, the SP for tone bursts is generally measured before the AP, because a contralateral reference electrode is employed. Therefore, in humans, substantial auditory brain stem response (ABR) activity may be present in the recordings after the AP, precluding measurement of the SP during that epoch. In animals, with use of invasive recording techniques, the response is larger, allowing use of an ipsilateral reference electrode, which essentially avoids interference by ABR activity. Consequently, the SP can be recorded during the plateau, or maximal, portion of the stimulus.

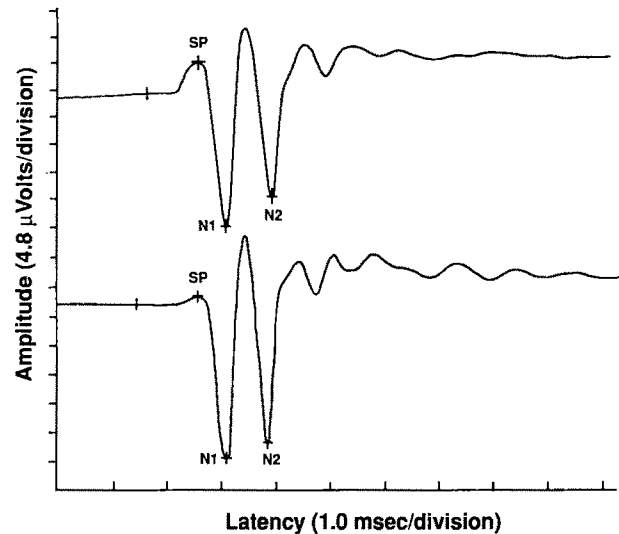


Fig 2. Electrocochleogram obtained with click stimulus in guinea pig 2 before (lower trace) and after (upper trace) induction of fistula. SP — summing potential.

In humans, for electrode placements commonly employed, the SP is generally negative in polarity, ie, in the same direction as the AP. For animals, the SP may be positive or negative, depending on the recording site in the bulla and the health status of the ear. In any species, for tone burst stimuli, a negative SP will tend to enhance measured AP amplitude. Conversely, a positive SP will tend to diminish measured AP amplitude, because SP activity will overlay AP activity.

Recordings were obtained for all stimuli before and after induction of a fistula at the round window via a facial recess approach. The induced lesion consisted of a single incision that exceeded half the diameter of the round window. The postfistula recording began within 10 minutes after lesion induction. Recordings for the 2,000-Hz tone burst stimuli were only obtained for the first 11 animals in the study. Use of this stimulus was then discontinued because of time constraints and the lack of any change noted in an analysis of the preliminary data.

RESULTS

Figure 2 shows the electrocochleograms obtained, using a click stimulus, for guinea pig 2 prior to and immediately after induction of the lesion. After induction of the round window fistula, the SP was markedly increased for guinea pig 2. The amplitude and morphology of the N1 waveform are similar to those of the prelesion condition. The results for this animal were not unusual, but representative of changes generally observed. The change in the SP/AP after lesion induction was generally obvious by visual inspection even before metrics were applied.

The SP amplitude versus AP amplitude is plotted for the click stimuli for all three levels in Fig 3. The increase in the SP/AP was significant at the .05 level for the 80-dB peSPL stimuli, and at the .01 level for

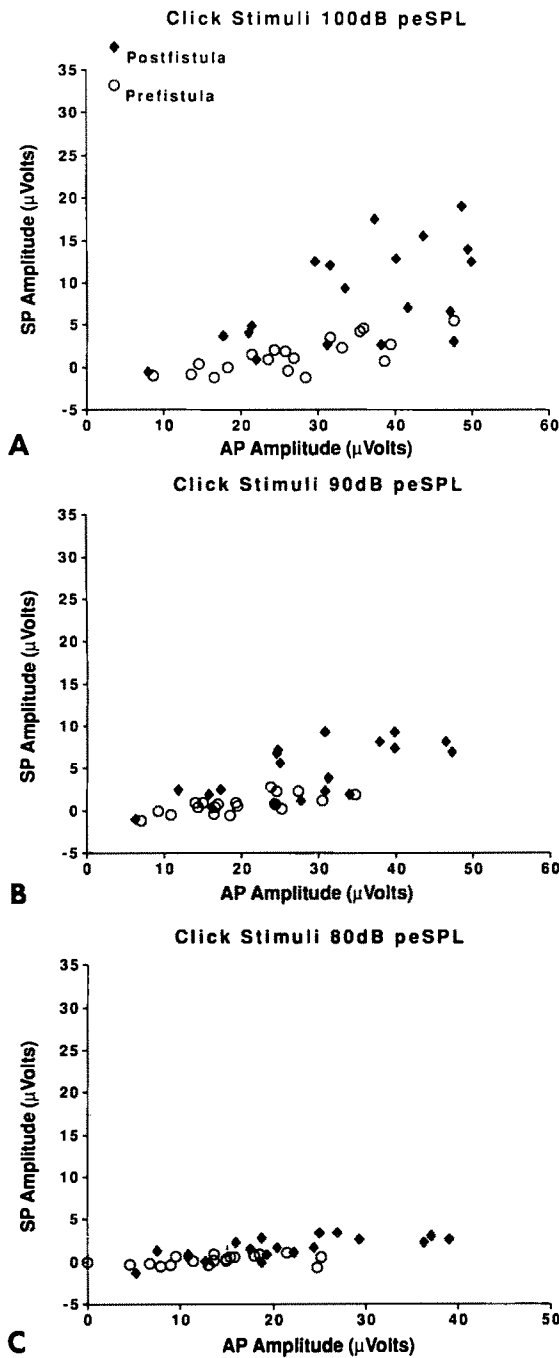


Fig 3. Scattergrams plotting summing potential (SP) amplitude as function of action potential (AP) amplitude for click stimuli. Open circles — individual data points before induction of fistula, closed squares — data obtained after fistula induction. A) Stimuli of 100 dB peak equivalent sound pressure level (peSPL). B) Stimuli of 90 dB peSPL. C) Stimuli of 80 dB peSPL.

the 90- and 100-dB peSPL levels (*t* test, analysis of matched pairs: $p = .0193$, $.0001$, and $.0001$, respectively).

The SP amplitude versus AP amplitude is plotted for the 8,000-Hz tone burst stimuli for all three levels in Fig 4. For each level, the increase in the SP/AP was significant at the .01 level (*t* test, analysis of matched pairs: $p = .0102$, $.0076$, and $.0014$, respectively).

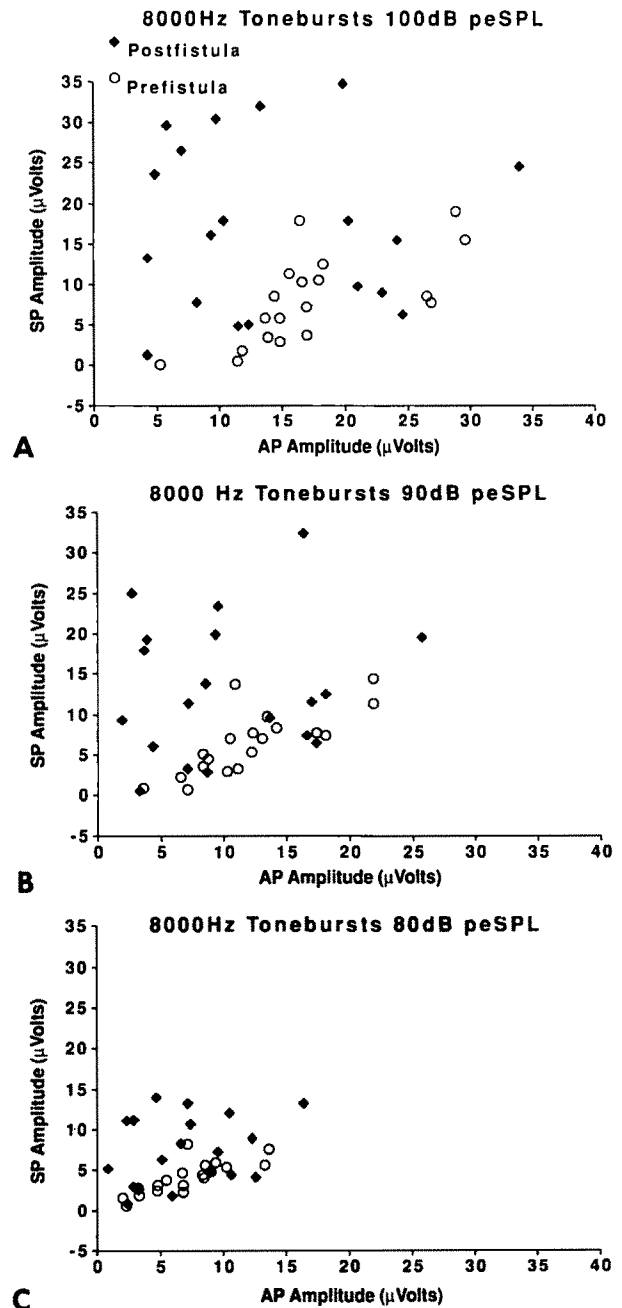


Fig 4. Scattergrams plotting summing potential (SP) amplitude as function of action potential (AP) amplitude for 8,000-Hz tone burst stimuli. Open circles — individual data points before induction of fistula, closed squares — data obtained after fistula induction. A) Stimuli of 100 dB peak equivalent sound pressure level (peSPL). B) Stimuli of 90 dB peSPL. C) Stimuli of 80 dB peSPL.

The SP amplitude versus AP amplitude is plotted for the 2,000-Hz tone burst stimuli for all three levels in Fig 5. For the 2,000-Hz tone burst stimuli, no significant change in the SP/AP occurred after fistula induction for the 80-, 90-, or 100-dB peSPL level (*t* test, analysis of matched pairs: $p = .7711$, $.5627$, and $.2914$, respectively).

Thresholds for the click stimuli or the 2,000-Hz and 8,000-Hz stimuli were not significantly changed

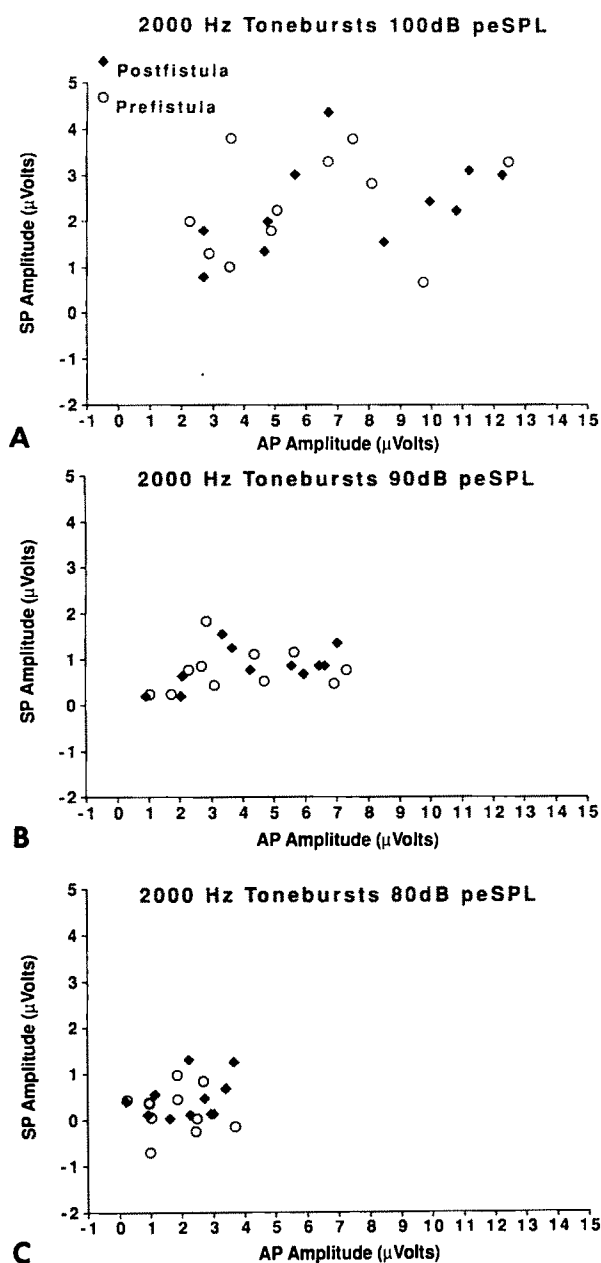


Fig 5. Scattergrams plotting summing potential (SP) amplitude as function of action potential (AP) amplitude for 2,000-Hz tone burst stimuli. Open circles — individual data points before induction of fistula, closed squares — data obtained after fistula induction. A) Stimuli of 100 dB peak equivalent sound pressure level (peSPL). B) Stimuli of 90 dB peSPL. C) Stimuli of 80 dB peSPL.

by the induction of perilymphatic fistula (*t* test, analysis of matched pairs: $p = .5426$, $.6761$, and $.7486$, respectively). The AP thresholds for the prelesion condition were as follows: click, mean = 30.63 dB peSPL and SD = 6.74; 2,000 Hz, mean = 73.8 dB peSPL and SD = 4.04; 8,000 Hz, mean = 33.95 dB peSPL and SD = 12.20.

Polarity of the SP was positive (relative to the negative AP) for the 8,000-Hz stimuli for all animals and all levels for both the prelesion and postlesion conditions. For 2,000 Hz, the SP was in-

variably positive for both the prelesion and postlesion conditions for the 90- and 100-dB peSPL stimulus levels. At the 80-dB peSPL level, 3 of the 11 animals tested with 2,000-Hz stimuli had a negative SP in the prelesion condition, but all were positive in the postlesion condition. For click stimuli at 80 and 90 dB peSPL, 6 of 19 animals had a negative SP in the prelesion condition, but only 1 had a negative SP in the postlesion condition. For click stimuli at 100 dB peSPL, 5 of 19 animals had a negative SP in the prelesion condition, but only 1 in the postlesion condition.

DISCUSSION

The primary difference in the findings for the prelesion and postlesion conditions is the increased SP/AP for the click and 8,000-Hz tone burst stimuli. One possible explanation for the increase in SP/AP after fistula induction is a change in the relative position of the basilar membrane or the intracochlear hydrostatic pressures. As perilymph leaks through the round window, a decrement in perilymphatic volume and possibly pressure could be expected. Consequently, the position of the basilar membrane could shift toward the scala tympani. The pressure change could have been partially offset by the flow of cerebrospinal fluid through the cochlear aqueduct. The significantly increased SP/AP, as a consequence of fistula induction, is consistent with the original hypothesis of this study.

Curiously, the increased SP/AP occurred only for the click and 8,000-Hz tone burst stimuli and not for the 2,000-Hz tone burst stimuli. A possible explanation for the difference in findings for the various stimuli may be differences in the structure of the basilar membrane between the more basal and apical turns. Although the anatomic differences, including width, stiffness, and density of innervation, are well known, the effects of the anatomic differences on physiologic and electrophysiologic variations, particularly under pathologic conditions, are not well understood.

Another possible explanation is the cable properties of electrical transmission in the cochlea. Electrical activity of the SP generated in the more apical turn would be more attenuated than activity from the basal turn by the time it reached the recording electrode. Consequently, any changes in the SP would be more difficult to measure for lower-frequency stimuli.

We did not find the consistent polarity reversals reported by Arenberg et al.⁸ The disparity in findings may be attributed to differences in methodology. Arenberg et al blocked the cochlear aqueduct and suctioned perilymph from the round window. In the present experiment, the cochlear aqueduct remained patent and no perilymph was suctioned. Consequently, the alteration in the pressure gradient across the basilar membrane was possibly less

in this study than in the aforementioned one.

However, both studies suggest that the SP/AP is sensitive to the creation of a perilymphatic fistula, both with and without occlusion of the cochlear aqueduct. Currently, perilymphatic fistula in humans is impossible to clearly diagnose without exploratory surgery. Therefore, the development of electrophysiologic measures to detect fistulas would be very useful, and further investigation is warranted. These data would suggest that an increased SP/AP may not be specific to Meniere's disease.

The absence of a threshold shift for any of the three stimuli initially appears to be in disagreement with earlier work. Differences in findings could have resulted from differences in methodology. Simmons et al⁹ reported a 35-dB threshold shift the day after induction of a perilymphatic fistula in cats. They also reported tissue reactions to the implanted electrode and the presence of middle ear fluid. They did not measure auditory threshold immediately after fistula induction, but the amplitude of the cochlear microphonic (CM) changed by an average of less than 6 dB. Axelsson et al¹⁰ reported development of hearing loss in guinea pigs 2 weeks after fistula induction, but also reported a high incidence of otitis media and hemorrhage of the round window. Weisskopf et al¹¹ reported an immediate decrease in CM amplitude after fistula induction, but did not actually measure threshold. McClure and Lycett¹² removed the entire round window membrane of cats and found an immediate 25-dB

decrement in threshold followed by an additional 35-dB decrement over time. Lamm et al¹³ reported a near-100% decrease in AP, ABR, and CM amplitude, but actively suctioned perilymph from the fistula. When the bulla was filled with Ringer's solution and perilymph was not suctioned, no change in auditory threshold occurred. Therefore, the findings of the present study, in which no threshold change occurred as a consequence of simple laceration of the round window membrane, are not necessarily in disagreement with earlier work.

Naturally, several caveats must be heeded when applying animal findings to a human population for both auditory threshold and SP/AP interpretation. In the guinea pig, the cochlear aqueduct is patent and allows for the flow of cerebrospinal fluid into the perilymphatic space. In human adults, the cochlear aqueduct may be occluded and may limit or prevent this flow. Consequently, in the human, an influx of cerebrospinal fluid may not be available to offset the leakage of fluid through a perilymphatic fistula. Another consideration is that this study looked only at the effect of an acute lesion. In humans, the lesions that are of clinical concern are often chronic or recurrent, and diagnostic evaluation may occur days, months, or even years after actual onset of the disorder. Diagnostic findings at that time may be different from those at the initial onset of the fistula. Nonetheless, these findings do suggest that further investigation is warranted, particularly in humans with perilymphatic fistula.

ACKNOWLEDGMENT — We are grateful to Steve Verhulst, PhD, for his assistance with statistical analysis.

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DETECTION OF HUMAN PAPILLOMAVIRUS INFECTION IN DISEASED AND NONDISEASED SITES OF THE RESPIRATORY TRACT IN RECURRENT RESPIRATORY PAPILLOMATOSIS PATIENTS BY DNA HYBRIDIZATION

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We examined 12 recurrent respiratory papillomatosis patients, who were undergoing treatment for recurrence of their disease, for the presence of human papillomavirus (HPV). Biopsies were obtained from their respiratory papillomas and nondiseased sites (NDS) of the respiratory tract: the nasopharynx, posterior tonsillar pillar, aryepiglottic fold, cervical trachea, intrathoracic trachea, and bronchi. The presence of HPV DNA was determined by using the ViraPap/ViraType DNA hybridization procedure. Two thirds of the patients were infected with HPV 6/11 in either the diseased papilloma or NDS: 50% of patients with papilloma specimens typed positive (6 of 12), and 40% of the patients typed HPV-positive in one or more biopsies from the NDS (4 of 10). No single NDS was more likely to be infected with HPV than any other. No oncogenic HPV types 16/18 or 31/33/35 were detected in the papillomas or NDS of these patients. Only patients with multiple, and not isolated, papilloma involvement were found to harbor HPV DNA in NDS; and 80% of those with infected NDS, compared to 20% of those without infected NDS, required a shorter (no more than 3 months) surgical treatment interval. Our results show that HPV infection frequently persists in adjacent, clinically normal sites, and suggest that the extent of NDS involvement may predict both the extent of disease and the likelihood of recurrence.

KEY WORDS — human papillomavirus, recurrent respiratory papillomatosis.

INTRODUCTION

The incidence of recurrent respiratory papillomatosis (RRP) in the United States is about 2,000 cases per year,¹ and the disease is accompanied by a high degree of morbidity and economic cost.^{2,3} It is considered the most common benign pediatric laryngeal tumor, with a high risk among children under 5 years of age.^{1,3-5}

Recurrent respiratory papillomatosis lesions show morphological changes typical of papillomaviral infection and are associated with the presence of human papillomavirus (HPV) types 6 and 11.⁵⁻⁹ These mucosal HPV types also are found in condylomata acuminata and other benign anogenital diseases. However, it also is important to evaluate RRP patients for the presence of other HPV types that are associated with high-grade genital intraepithelial neoplasias and carcinomas, since their respiratory papillomas can develop dysplasia and carcinomas in the absence of known risk factors.¹⁰⁻¹² Previous studies have examined small numbers of papillomas for HPV-16 and -18, but not for other mucosal-related oncogenic types, such as HPV-31, -33, or -35.^{10,13,14}

Another aspect of RRP that is not fully under-

stood is the source of the virus that leads to recurrence. The clinical pattern of recurrence in RRP patients, like that of genital condylomas,¹⁵ could be explained by the persistence of HPV infection in morphologically normal tissue adjacent to papillomas.^{5,6} Abramson et al⁵ and Steinberg et al⁶ evaluated HPV-6 and -11 in nondiseased sites (NDS) from RRP patients who were in remission, and in whose papillomas they previously detected viral infection. They found the virus in some NDS of the respiratory tract, suggesting that papilloma recurrence could be due to activation of clinically inapparent infection rather than to reinfection with the virus. It also is possible that NDS may harbor oncogenic viral types that would subsequently lead to malignant respiratory tumors. To date, no published studies have evaluated additional HPV types in NDS of RRP patients.

The purpose of this study was to provide baseline data in a series of young RRP patients regarding 1) HPV frequency and types by using probes specific for HPV-6 and -11, as well as the mucosal oncogenic types 16, 18, 31, 33, and 35, in respiratory papillomas and in NDS that were biopsied concurrently

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Presented at the meeting of the American Academy of Otolaryngology-Head and Neck Surgery, San Diego, California, September 9-13, 1990.

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TABLE 1. HPV INFECTION IN RESPIRATORY PAPILOMAS AND NONDISEASED RESPIRATORY SITES OF RRP PATIENTS

Age at Biopsy (y)	Age at Onset (y)	Sex	Isolated Versus Multiple Sites	Treatment Interval (mo)	HPV DNA Hybridization Results*						
					Papilloma	NP	TP	AF	CT	IT	BR
2	1	M	M	≤3	+	NS	NS	—	+	NS	NS
3	1	M	I	>3	—	NS	NS	NS	NS	NS	NS
5	1	M	I	>3	—	—	—	—	NS	NS	NS
8	2	F	M	≤3	+	NS	NS	NS	NS	NS	NS
8	2	F	I	>3	—	—	—	—	—	—	—
10	2	F	I	>3	+	—	—	—	—	—	—
11	1	M	M	≤3	—	+	—	—	—	—	—
12	<1	M	M	≤3	+	+	—	—	—	—	—
14	5	F	I	≤3	—	—	—	—	NS	NS	NS
19	<1	M	M	≤3	—	—	+	—	—	+	+
19	13	F	I	>3	+	—	—	—	—	NS	—
29	20	M	I	>3	+	—	NS	—	—	—	—

HPV — human papillomavirus, RRP — recurrent respiratory papillomatosis, NP — nasopharynx, TP — posterior tonsillar pillar, AF — aryepiglottic fold, CT — cervical trachea, IT — intrathoracic trachea, BR — bronchus, NS — no specimen.

*All positives were for HPV 6/11.

from the same patient, 2) the association between HPV infection and the clinical behavior of disease, and 3) the identification of risk factors associated with a diagnosis of and recurrence of RRP.

METHODS

This study included 12 RRP patients who were treated in the Department of Otolaryngology at The University of Iowa Hospitals. Because of potential etiologic differences associated with endogenous steroid hormone exposure, cases were divided into childhood-onset (10 patients under 12 years of age), and adult-onset (2 patients equal to or over 12 years of age).

Tissues evaluated in this study were biopsied between 1989 and 1990, from respiratory papillomas (12 patients) and various NDS in the respiratory tract of these patients (10 patients): nasopharynx, posterior tonsillar pillar, aryepiglottic fold, cervical trachea, intrathoracic trachea, and bronchi (Table 1). The patients were undergoing treatment for recurrence of their disease. Specimens were not collected at all NDS from every case, primarily because of concern for lengthy anesthesia in those patients. All respiratory papillomas and NDS were biopsied concurrently from each patient during his or her latest operation.

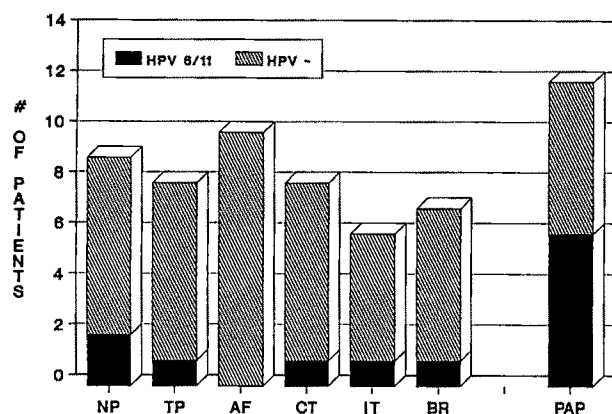
Laryngoscopic biopsies of papilloma and NDS tissues were collected for HPV DNA assessment during the patient's appointment for treatment of latest recurrence. Only one papilloma specimen was tested for HPV DNA assessment even if there was multiple site involvement. Most papilloma specimens were biopsied from the larynx; one papilloma specimen was taken from the uvula. Among the five patients with multiple site involvement, three had extensive disease identified at their initial diagnosis, and all of these patients had multiple papilloma involvement during their current treatment and biopsy for HPV DNA assessment.

Severity of RRP disease was determined by the

frequency with which a patient required a laser laryngoscopy to maintain an airway (3 months or less versus more than 3 months). Extent of papilloma disease was defined as either 1) multiple sites, ie, more than one site of active disease in the respiratory tract at the time of biopsy, or 2) isolated, ie, one site of active disease (Table 1). Active disease was the presence of a site in the airway that demonstrated active papilloma growth; inactive disease was defined as that part of the airway in which biopsies demonstrated HPV DNA, but in which there was no active papilloma growth.

The HPV DNA hybridization technique used to determine HPV infection was the ViraPap/ViraType (Life Technologies, Gaithersburg, Md). The HPV types assessed were 6/11, 16/18, and 31/33/35. These techniques are comparable in sensitivity and specificity of HPV DNA detection to the established Southern blot hybridization protocol¹⁶⁻¹⁸ (also our unpublished data), which can detect 0.1 copy per cell. The ViraPap kit is approved by the Food and Drug Administration as a diagnostic test for HPV infection in cervical smears. In the first test (ViraPap) of this proprietary procedure, all samples are hybridized to a mixed ³²P-labeled complementary RNA probe specific for HPV types 6, 11, 16, 18, 31, 33, and 35. In the second test (ViraType), positive or ambiguous samples are retested against three sets of probes that subclassify these HPV types into types 6/11, 16/18, and 31/33/35. Ambiguous samples from the ViraPap screen were considered positive only when they fell clearly into an HPV group on the ViraType test.

In addition to collecting specimens for HPV DNA from each patient, we also reviewed their medical histories to determine age at onset, surgical intervals, the initial diseased site, current diseased sites, treatment type, and characteristics of remission. Risks associated with HPV infection were assessed by a patient questionnaire concerning 1) sociodemographics, 2) parental and sibling history of RRP



Frequency of human papillomavirus (HPV) infection in papillomas and nondiseased respiratory tract sites. NP — nasopharynx, TP — posterior tonsillar pillar, AF — aryepiglottic fold, CT — cervical trachea, IT — intrathoracic trachea, BR — bronchus, PAP — papilloma.

or other HPV-related diseases, particularly those noted during pregnancy of the RRP patient's mother, 3) birth order, 4) delivery type (vaginal or cesarean section), 5) sexual history (of the parents in childhood-onset RRP, or of the patient in adult-onset RRP), 6) initial RRP symptoms, 7) immune-related disorders, and 8) characteristics of treatments and remissions. Patients (at least 12 years old) or their parents (patients under 12 years old) completed the questionnaire.

RESULTS

Clinical and HPV DNA Findings. The distribution and anatomic site of the tissues collected are shown in Table 1. Overall, 67% of the RRP patients were HPV-positive. The DNA hybridization results showed that only HPV-6/11 was detected in any of the specimens, whereas HPV-16/18 or HPV-31/33/35 were not. Of the papilloma biopsies ($n = 12$), 50% were positive for HPV-6/11 (see Figure).

Half of the HPV-positive papillomas were from patients with isolated involvement and the other half were from patients with multiple-site involvement. Whereas HPV DNA was detected in 60% (three of five) of the patients with multiple papilloma sites, fewer than half (43% or three of seven) of the patients with isolated papillomas were found to have viral DNA.

Among patients who had biopsies of NDS ($n = 10$), 40% were detected with HPV DNA — in all cases HPV-6/11 (Table 1). This detection rate is only slightly lower than that seen in the papilloma tissue. All anatomic locations except the aryepiglottic fold harbored HPV infection (see Figure). No NDS was significantly more likely to be identified with HPV infection than others.

All patients who had multiple sites of papilloma involvement were positive for HPV infection in their NDS. In contrast, those with isolated papilloma involvement were all HPV-negative in their

TABLE 2. SEVERITY OF DISEASE AND PRESENCE OF HPV INFECTION IN NONDISEASED SITES

HPV DNA Result	Surgical Treatment Interval			
	≤3 mo		>3 mo	
	No.	%	No.	%
HPV-6/11-positive	4	80	0	0
HPV-6/11-negative	1	20	5	100

There was no specimen in one isolated and one multiple papilloma case; hence, number of patients shown is 10.

HPV — human papillomavirus.

NDS. All HPV-positive tissues in NDS were identified in males. The presence of HPV-6/11 in papillomas was not associated with severity of disease, ie, frequency of papilloma recurrence. In contrast, a shorter surgical treatment interval was associated with a higher probability of finding HPV infection in the NDS (Table 2): 80% of those with an interval of 3 months or less compared with 0% of those with a longer interval (more than 3 months) were positive for HPV-6/11.

Two types of treatment have been administered to these RRP patients since their initial diagnosis: 1) carbon dioxide laser versus 2) laser plus α -interferon. Treatments were evaluated in association with the frequency of HPV infection, since they may influence HPV activation. However, treatment type was not associated with likelihood of HPV infection in either the papillomas or NDS, regardless of extent or severity of disease at the time of biopsy.

Among the four patients with a prior tracheotomy, two with documented disease in their tracheo-bronchial sites (cervical trachea, intrathoracic trachea, and bronchus) were HPV-positive: one had pulmonary involvement and one did not. Two other patients with a prior tracheotomy were HPV-negative: again, one had lung involvement and the other did not. Thus, these findings showed no association between prior tracheotomy and subsequent risk of HPV infection in the inferior airway. However, there is no way to know if tracheotomy would have an effect on transmission of HPV infection to the lower airway among those who were infected with HPV, since we did not have information regarding HPV status prior to their tracheotomy.

Characteristics of RRP Patients. There were slightly more males than females (58% versus 42%) within each age at onset group (Table 1). There was an equal frequency of males and females whose respiratory papillomas tested HPV-positive (Table 1). Males with multiple papillomas had HPV infection in the NDS as well. No nondiseased tissue biopsies were available from the one female with multiple-site papillomatosis for comparison.

Most patients (83% or 10) developed disease as children. Since hormones are known to influence HPV activation, we examined whether age at onset was associated with likelihood of HPV infection in

papillomas or NDS. We found no association between age at onset and probability of HPV infection, extent of disease, active versus inactive disease areas, or severity of disease. Presence of genital HPV-related diseases in the parents of these RRP patients also was documented in 25% of the parents; none had respiratory papillomas. Of the patients in whom maternal delivery type was known ($n = 10$), all were delivered vaginally. There was no relationship between delivery type and age at onset, extent of disease, or HPV infection.

Patients were more likely to be firstborns or only children (75%), but there was no association between this characteristic and RRP disease parameters. No immune-related or genetic diseases were identified. Siblings (biologic or unrelated) uniformly did not develop the disease. A large number of the patients were adopted or living in disrupted households (42%). The educational level of the parents or RRP patients with ≥ 12 years was 87.5%; 75% were white (compared with 98% for the state), with one patient each Hispanic, black, and Asian.

DISCUSSION

We found a high frequency of HPV infection in NDS in our series of RRP patients. The virus was identified in virtually all NDS in patients who had severe papillomatosis at the time of their latest recurrence. In contrast, HPV DNA was not found in NDS biopsies from patients with less severe (no more than 3-month treatment interval) papilloma involvement. Furthermore, HPV was more likely to be detected in individuals with multiple compared with single papillomas. These findings suggest that 1) the presence of HPV infection in NDS is associated with respiratory papilloma recurrence and 2) the extent of HPV infection beyond the larynx may predict severity of disease and thus prognosis.

Our results do not support the concept that extensive eradication of only visible papillomas in severe cases will cure the patient or reduce the surgical interval. Since patients with a history of frequent recurrences or more severe disease appear to have a higher probability of HPV infection in NDS, treatment of these areas may be needed to increase the remission intervals. This conclusion is further substantiated by studies of HPV-6/11 infection in genital condylomas. Among those who receive laser treatment for this HPV-related disease, infection is detected in clinically normal tissue adjacent to the margins of these lesions, and this infection is considered to be the source of subsequent recurrence.¹⁵ We have shown that nearly all clinically normal respiratory sites can harbor the virus. Therefore, RRP patients may benefit from HPV DNA assessment of other areas in the airway at their initial diagnosis to guide treatment.

Our findings indicate that neither respiratory papillomas nor NDS are associated with oncogenic

HPV types in young RRP patients. Several authors have reported that premalignant and malignant respiratory tumors that developed in RRP patients harbored HPV-6 or -11, while other types, HPV-16 and -18, were absent.¹⁰⁻¹³ Our results confirm and extend these findings. We examined papillomas and NDS tissues for additional oncogenic types frequently identified in mucosal lesions (HPV-31, -33, and -35) and did not detect infection with these viral types.

One of the risks that may contribute to RRP is birth order. Our observation that firstborns and only children were most likely to develop RRP has been noted by others as well (B. Steinberg and H. Kashima, personal communication, 1991), but the paper interpretation of this finding is unclear. Other potential risks of RRP that we examined were not associated with recurrence, extent of disease, or HPV infection. However, this study may not have the ability to detect minor increases in risk because of small sample size.

Another potential risk of RRP, parental HPV infection during pregnancy that leads to vertical transmission of HPV in offspring, is still not well documented. Only 25% of the parents in this series of RRP patients stated that they had a history of a genital HPV-related disease, but regardless of technique used, DNA hybridization has detected asymptomatic HPV infection in 15% to 28% of adults, including Pap-negative pregnant women.^{19,20} Since the parents were not tested prior to birth of the RRP patients in this study, it is unclear whether vertical transmission occurred. Prospectively designed studies using molecular techniques are critical to identifying the source of HPV DNA that may cause infection in their newborn.²⁰ We and others have shown that the virus can be transmitted to newborns in the absence of a positive maternal HPV DNA test performed prior to delivery, or a history or clinical manifestation of HPV-related genital disease during pregnancy.^{20,21} The HPV DNA-positive infants showed no clinical signs of an HPV-related disease at birth.

Additional investigations are needed to compare RRP patients with age- and sex-matched nondiseased controls to better understand the role of HPV and other potential risks in the causation of papillomatosis. Other risk factors may be necessary for the virus to cause RRP and may be identified by comparing the medical history and life-style factors between the two groups. Studies should determine whether HPV infection is absent in respiratory tissues of healthy persons, or whether the virus exists in nondiseased individuals as well. These investigations will be facilitated by highly sensitive HPV detection assays based on DNA amplification by the polymerase chain reaction. Despite the unexpectedly high percentage of HPV-positive NDS biopsies in this study, the relatively large number of HPV-neg-

active papilloma samples may reflect the limitations of HPV detection in small lesions by the ViraPap/ViraType hybridization test. The use of standardized polymerase chain reaction assays for HPV DNA detection should resolve this problem.²² We currently are evaluating the procedure for HPV detection in RRP and NDS biopsies.

Prospectively designed research also is needed to investigate both nondiseased tissue from various

anatomic sites in the airway and respiratory papillomas sampled concurrently in a series of RRP patients. Tissues should be compared for the presence, extent, and types of viral infection at different sites. The information would provide baseline data useful in reexamining changes in disease behavior associated with treatment, HPV types, changes in HPV infection in NDS, risk factors for RRP, and risk of respiratory dysplasia and cancer development.

ACKNOWLEDGMENTS — We thank Bettie Steinberg, PhD, for her review of the manuscript, and Thomas H. Haugen, MD, PhD, and Richard D. Anderson for their advice on hybridization procedures.

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TEMPORAL BONE FINDINGS IN KERATITIS, ICHTHYOSIS, AND DEAFNESS SYNDROME

CASE REPORT

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In 1981, the term KID syndrome was suggested for patients with congenital ichthyosis associated with deafness and keratitis. We had a chance to examine the temporal bone of an infant with this syndrome. This patient showed no auditory brain stem response in either ear. Temporal bone studies revealed cochleosaccular abnormality. These findings are offered as a possible explanation for the patient's deafness. The pathologic inner ear findings of congenital deafness syndromes associated with ichthyosis have been heretofore reported in Refsum's syndrome and in a case with universal alopecia. In these cases, the temporal bone pathologic findings were a result of cochleosaccular abnormality. From our case and previous reports, it is suggested that the deafness associated with congenital ichthyosis might be the result of cochleosaccular abnormality.

KEY WORDS — congenital ichthyosis, deafness, KID syndrome, temporal bone.

INTRODUCTION

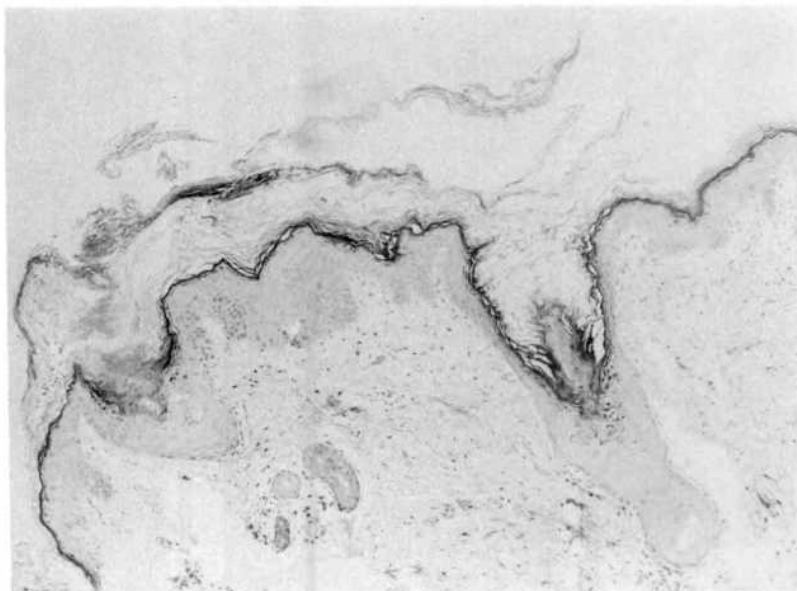
In 1915, Burns¹ described a patient with "generalized congenital keratoderma" associated with keratitis and deafness. Since that time, at least 25 similar patients have been reported.^{2,3} The clinical features of these cases include distinctive ichthyosis, vascularizing keratitis, hearing loss, and recurrent bacterial and fungal infections of the skin. In 1981, Skinner et al³ proposed the term KID syndrome for these cases to emphasize the characteristic clinical features: keratitis, ichthyosis, and deafness.

According to previous reports,^{2,3} the type of hearing loss in this syndrome is sensorineural. But the histopathologic changes in the inner ear are not known. In this report, we describe the temporal bone findings of a patient with this syndrome who died of sepsis.

CASE REPORT

Clinical Course. A 2-month-old girl presented with erythrokeratodermalike ichthyotic skin, vascularizing keratitis, and deafness. She had been the

Fig 1. "Basket-weave" hyperkeratosis of epidermis (H & E, original x10).



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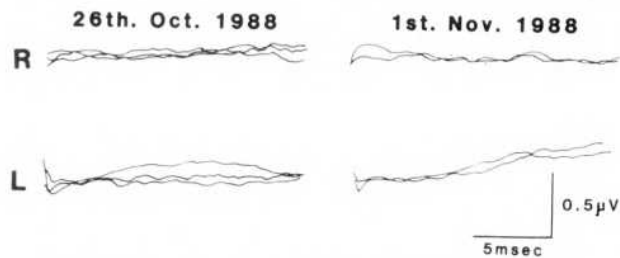


Fig 2. Auditory brain stem response testing. There was no response even at 100 dB on 15th and 21st days of life. Click sound of 0.1 milliseconds at 4,000 Hz was used.

product of an uncomplicated pregnancy, labor, and delivery. There was no history of deafness or skin disease in the family, and the patient's siblings were normal. She was admitted to Saitama Children's Medical Center on the first day of her life as dry, erythematous, scaly skin lesions were observed at birth. Results of physical examination revealed marked generalized skin dryness and erythematous skin lesions. The palms and soles showed prominent hyperkeratosis and fissures. All of her nails were thickened. No hair was present on the scalp, nor did she have eyebrows or eyelashes. Skin biopsy obtained from the forearm showed hyperkeratosis with a basket-weave pattern and follicular plugging (Fig 1).

Corneal pannus was observed in both eyes, and deafness was noted at the age of 15 days. On the 31st day, skin infection occurred. In spite of antibiotic therapy, the skin infection spread and the patient died of sepsis and pneumonia on the 51st day of life. Ototoxic drugs such as aminoglycoside were not used throughout the course. Autopsy was done 2 hours after her death. The laboratory data are presented below. A chromosome study showed no abnormality, and no congenital metabolic disorders were found. Before she developed the skin infection, no abnormality was noted in the serum or urine studies. A computed tomographic scan of the

brain and an electroencephalogram showed no abnormality. There was no abnormality that suggested a viral infection such as maternal rubella in the serum studies of the mother and infant.

Otologic Findings. Erythrokeratoderma-like ichthyotic changes were observed on the skin of the external auditory meatus, but the eardrum was normal. No effusions were seen in the middle ear. Auditory brain stem response (ABR) testing was performed twice, but no positive responses were obtained in either ear even at 100 dB hearing level (Fig 2).

TEMPORAL BONE FINDINGS

Left Ear. The bony structures were normal. The middle ear mucosa was hypertrophic, with submucosal infiltration of the lymphocytes. The stapes footplate was normal. The malleus and incus were normal in structure. The tympanic membrane was lost in preparation. The facial nerve was normal. The semicircular canals, including the membranous labyrinth, were normal. The cupulae and sensory epithelium did not show any abnormality. The utricle, endolymphatic sac, and cochlear aqueduct were all normal.

The saccular membrane was collapsed onto the outer fibrous connective tissue layer of the envelope. The otolithic membrane within the fibrous envelope was adherent to the macula of the saccule, and the sensory epithelium was absent (Fig 3).

There was very poor preservation of the hair cells. The cells of the organ of Corti were immature. The inner and outer hair cells were present. The cells of the inner sulcus were preserved and did not form an inner sulcus. The tunnel of Corti had developed. Reissner's membrane was displaced to the organ of Corti. A membrane was present from the basal membrane to the spiral prominence. The

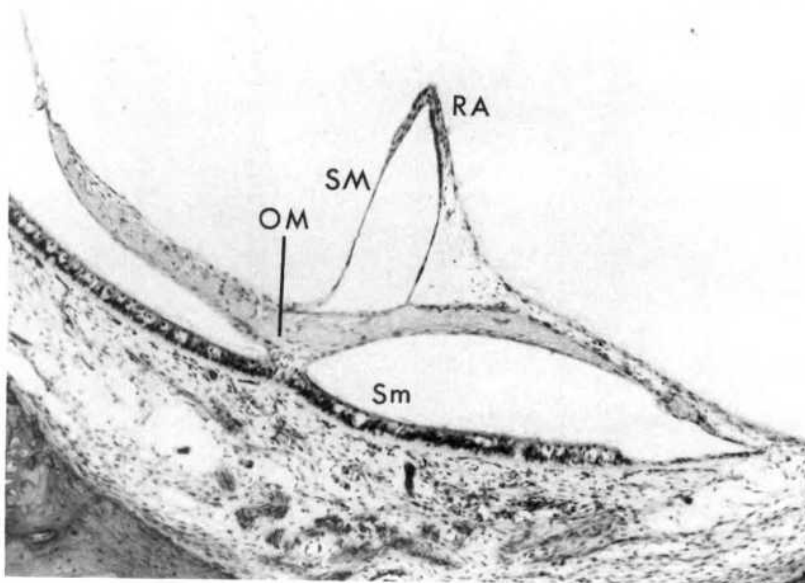
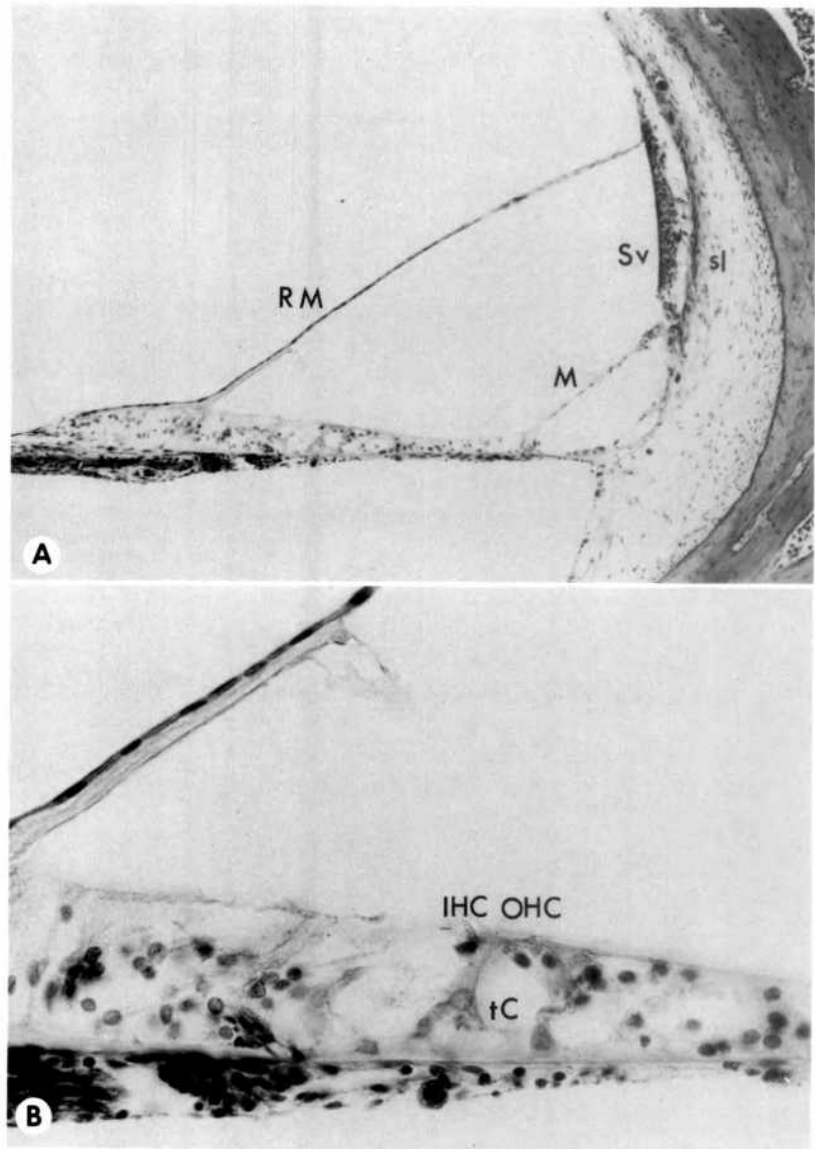


Fig 3. Saccular membrane (SM) is collapsed except for reinforced area (RA; original $\times 12.5$). Adhesion of otolithic membrane (OM) to macula of saccule (Sm) is noted.

Fig 4. Cochlear findings of middle turn. A) Reissner's membrane (RM) is displaced to organ of Corti (original x12.5). Stria vascularis (Sv) is displaced from spiral ligament (sl). There is membrane (M) stretching from basal membrane to spiral ligament. B) High-power view of organ of Corti shows preservation of inner hair cells (IHC), outer hair cells (OHC), and tunnel of Corti (tC; original x40).



stria vascularis was displaced from the spiral ligament, but this finding might have been due to post-mortem changes. The deposition of melanin in the stria vascularis was advanced for the patient's age (Fig 4). The spiral ganglion cell population was normal.

Right Ear. The histologic findings were similar to those in the left ear.

COMMENTS

In summary, the inner ear anomaly in this case was as follows. The organ of Corti was immature, similar to that at about 20 weeks of gestation, the stria vascularis was degenerated, and the saccules showed poor innervation. The utricle and semicircular canals were normal. These findings could be classified as reflecting cochleosaccular abnormality.

On the basis of the findings in the inner ear and histopathologic changes in the skin and cornea, the genesis of which is ectodermal, it might be sug-

gested that KID syndrome is derived from a systemic developmental disorder in the embryonal stage.

Congenital deafness with congenital ichthyosis is found in various syndromes, such as Refsum's disease and Rud's syndrome. The histopathologic study of the inner ear in Refsum's disease was done by Rake and Sanders,⁴ Hallpike,⁵ and Igarashi et al,⁶ and in an infant with universal alopecia by Myers et al.⁷ They found that the major peculiarity in these cases was cochleosaccular abnormality. Myers et al described two cases of hearing loss associated with ichthyosis and suggested a new dermatologic syndrome associated with congenital hearing loss. The first case was of a 5-year-old boy whose audiogram and clinical features only were reported. The second was of a newborn baby. In this case, they reported temporal bone findings. The first case was later designated KID syndrome by Skinner et al³ in 1981. Since Myers et al did not mention ophthalmologic findings in the second

case, it is unclear whether it was KID syndrome. The findings of our case and that of Myers et al were similar in the collapse of the saccular membrane, adherence of the otolithic membrane, poor innervation of the organ of Corti, and displacement of Reissner's membrane. Myers et al did not mention the deposition of melanin in the stria vascularis or the membrane from the basal membrane to the spiral prominence that were found in our case.

The main peculiarity in our case, in Refsum's disease, and in the case of Myers et al is cochleosaccular abnormality. Therefore, it might be concluded

that the histopathologic changes in patients with congenital deafness associated with congenital ichthyosis represent a cochleosaccular abnormality.

There was no ABR in either ear even at an intensity of 100 dB hearing level. This lack of response may be explained by the histopathologic abnormality of the inner ear, the immaturity of the organ of Corti, and the displacement of the stria vascularis from the spiral ligament, which might cause profound sensorineural hearing loss leading to the absence of an ABR.

ACKNOWLEDGMENTS — We thank Professor Tetsuo Ishii, Tokyo Women's Medical College, for his suggestion on temporal bone findings and Emi Saitou and Masako Igarashi for their help in preparation of the temporal bone specimens.

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INTERNATIONAL HEARING AID CONFERENCE GENERAL ANNOUNCEMENT AND CALL FOR PAPERS

An International Hearing Aid Conference will be held June 15-17, 1993, at The University of Iowa, Iowa City. For information on registration and accommodation, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231, Fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, Fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

MINUSCULE SUBMUCOUS CLEFT PALATE CADAVER STUDY

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Otitis media is almost universal in cleft palate patients, at least during infancy. A lesser cleft manifestation, the occult submucous cleft palate, is identifiable in living patients by surgical dissection or flexible fiberoptic nasopharyngoscopy. We addressed the hypothesis that an even more subtle form of submucous cleft palate, involving both an abnormal musculus levator veli palatini and an abnormal musculus uvulae, is associated with otitis media. We studied 35 adult human cadaver specimens for histologic and infrared photographic transillumination evidence of what we have identified as the minuscule submucous cleft palate. None of the specimens had evidence of clinical otitis media, or clinical abnormality of the palate. Approximately one fifth of the specimens had evidence of minuscule submucous cleft palate: minimal bulk of the musculus uvulae and haphazard organization of the fibers of the musculus levator veli palatini. These data support the nasopharyngoscopic inference that in occult submucous cleft palate, there is both hypoplasia of the musculus uvulae and abnormal orientation of the fibers of the musculus levator veli palatini. Although not significant statistically, a trend was suggested for minuscule submucous cleft palate to be associated with indicators of prior otitis media.

KEY WORDS — cleft palate, otitis media.

INTRODUCTION

Patients with overt cleft palate almost always have otitis media, at least during infancy. Cleft palate patients have anatomically different eustachian tubes¹ that presumably contribute to the occurrence of otitis media. Submucous cleft palate and even isolated bifid uvula are thought by some to be a minimal expression on a continuum of cleft palate manifestations.² Anatomic eustachian tube differences have been described in persons without clefts who have otitis media.³ Peculiarly, bifid uvula is apparently not associated with an excess occurrence of otitis media.^{4,5} Nevertheless, a more subtle manifestation of soft palate cleft, ie, no abnormality apparent at general clinical examination, has been associated with both otitis media and velopharyngeal insufficiency.⁶ The so-called occult submucous cleft palate, which is identifiable in living patients by surgical dissection^{7,8} or flexible fiberoptic nasopharyngoscopy,⁹ may be part of the anatomic differences involving the eustachian tubes of persons bothered by otitis media.^{9,10}

The classic submucous cleft palate is usually considered to have some combination of three intraorally visible stigmata: bifid uvula, muscular diathesis of the soft palate, and bony defect of the hard palate.¹¹ The identification, problems, and incidence of the classic and occult submucous clefts are controversial.^{6,7,11} The occult submucous cleft palate involves abnormal velar musculature, described both as less bulk of the musculus uvulae and as abnormal insertion of the musculus levator veli palatini. The deficiency in the musculus uvulae has been inferred endoscopically^{12,13} and the abnormality of

the musculus levator veli palatini has been noted at surgical dissection.^{7,8}

This study addressed the hypothesis that otitis media is associated with a non-clinically identifiable form of occult submucous cleft palate that we term minuscule submucous cleft palate. We sought information that might help to define the pathogenesis of otitis media. Our idea was that minuscule submucous cleft palate would involve both an abnormal musculus levator veli palatini and an abnormal musculus uvulae. Thirty-five cadavers with macroscopically normal palates were studied. We predicted the minuscule submucous cleft palate to be comparatively thin, to lack interdigitating fibers of the levator veli palatini muscle, to have a small musculus uvulae, and to have a midline that was relatively translucent. Evidence of minuscule submucous cleft palate was sought by gross thickness, infrared transillumination, and histologic determinations. Two separate indicators of prior otitis media were used: smallness of temporal bone pneumatization, and scarring of the tympanic membranes.^{14,15}

MATERIALS AND METHODS

SPECIMENS

Thirty-five formalin-fixed adult heads were provided by the Anatomy Department. All were from persons who antemortem had bequeathed their bodies to science; most were white, the remainder black. No specific racial, age, or sex information was available. Using standard criteria of physical anthropology, 30 of the 35 specimens could be categorized as to sex: 15 males and 15 females. No information on otologic history was available.

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A summary of this work was presented as a poster at the meeting of the American Academy of Otolaryngology-Head and Neck Surgery, Washington, DC, September 25-29, 1988.

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TABLE 1. SUMMARY OF PARAMETERS, TECHNIQUES, REPEATABILITY, AND FINDINGS OF SOFT PALATE SPECIMENS

Parameter	Technique	Repeatability	Findings
Soft palate thickness	Calipers	Not checked	Range 6.3-17.2 mm, mean 11.4, bimodal distribution
Overall translucency	Infrared photography	$\kappa = .50$	Translucent 1, intermediate 18, opaque 7, inconsistent 9
Midline opaqueness	Infrared photography	$\kappa = .87$	Band absent 11, present 22, inconsistent 2
Midsagittal fibrosis	Coronal histology	$\kappa = .93$	Not fibrotic 10, fibrotic 24, inconsistent 1
Musculus levator veli palatini	Coronal and midsagittal histology	$\kappa = .84$	Haphazard 7, organized 26, inconsistent 2
Musculus uvulae	Midsagittal histology	$\kappa = .57$	None 2, microscopically 1, few macroscopically 7, obvious macroscopically 15, inconsistent 10
Musculus palatoglossus	Midsagittal histology	$\kappa = .43$	Fibers absent 13, present 12, inconsistent 10
Salivary glands	Coronal histology	Not checked	Sparse 4, clusters 18, large clusters 9, abundant 4

INDICATORS OF PRIOR OTITIS MEDIA

Two separate indicators of prior (presumably childhood) otitis media were used: smallness of temporal bone pneumatization, and scarred tympanic membranes. (At subsequent dissection of the temporal bones, no specimen was found to have evidence of clinical otitis media.)

Mastoid Size. Law lateral radiographs were used to describe the extent of temporal bone pneumatization. The outline of pneumatization on the radiographic image was independently traced onto paper three times, and each tracing was measured by planimetry twice; the mean of the six determinations for size of each mastoid was used for data analysis. In contrast to Diamant's method¹⁶ of excluding the antrum region on the tracings, this region was included.¹⁷ The mean of the right and left areas was considered the pneumatization size of each specimen.^{10,14}

Tympanic Membrane Appearance. Tympanic membrane normality was assessed by a photographic technique.¹⁵ The pictures were made with a 35-mm camera having automatic exposure time, through a 0° Hopkins rod telescope. The ear canals had been cleansed with water irrigation and suction. The Kodacolor VR-G film had a speed of ISO 200. The magnification of the tympanic membrane on the print film was approximately 2. There were 66 photographs from 34 heads available for study. The tympanic membrane photographs were twice presented separately to an experienced otolaryngologist, who sorted the photographs into groups: "normal" tympanic membranes, "abnormal," and "cannot determine." The intraobserver repeatability was good: $\kappa = .62$. (The κ statistic corrects for random agreement.¹⁸) Only the photographs of ears consistently labeled normal or abnormal were used for data analysis. Heads were considered tympanoscopically normal if both the left and right tympanic membranes were considered normal at both of the sorting sessions. Specimens were considered tympanoscopically abnormal if at least one (right and/or left) tympanic membrane was labeled abnormal at both of the sorting sessions.

Congruence and Symmetry of Otitis Indicators. The heads with large mastoids generally had normal tympanic membranes ($p < .02$). The mean area of

pneumatization was 11.02 cm² (range 1.5 to 20.9, SD 3.67). Seven tympanic membranes were categorized as scarred and 46 as normal. Right-left symmetry of area of mastoid pneumatization was found ($r = .69$, $p < .001$). For the 20 cadavers with both left and right tympanic membranes consistently categorized, symmetry was suggested ($\phi = .32$, $p < .2$).

SOFT PALATE PREPARATION AND STUDY

The entirety of the soft palate including the contiguous oral mucoperiosteum was dissected; the superior soft tissue dissection was directly superior to the border of the hard palate. The posterior border of the hard palate did not exhibit any suggestion of notching in any of these specimens. Three separate types of studies were done to each soft palate: gross thickness, transillumination, and histologic examination (Table 1).

Thickness. The cephalocaudal (superior-inferior) thickness of each palate was measured with a spreading caliper (Fig 1).

Transillumination. The transillumination technique was photographic infrared. The film was Kodak black and white High Speed Infrared, sensi-

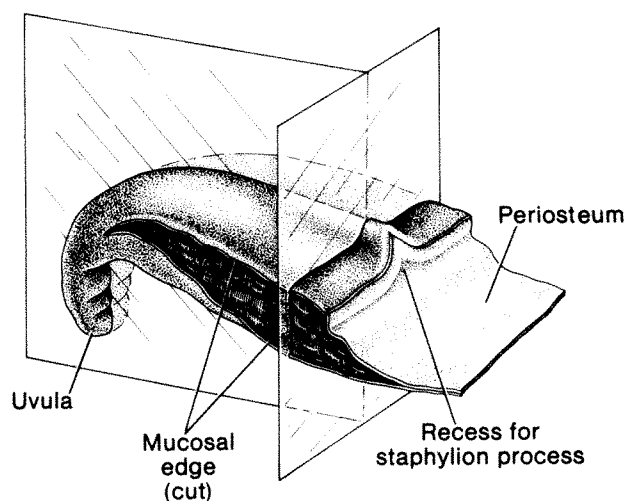
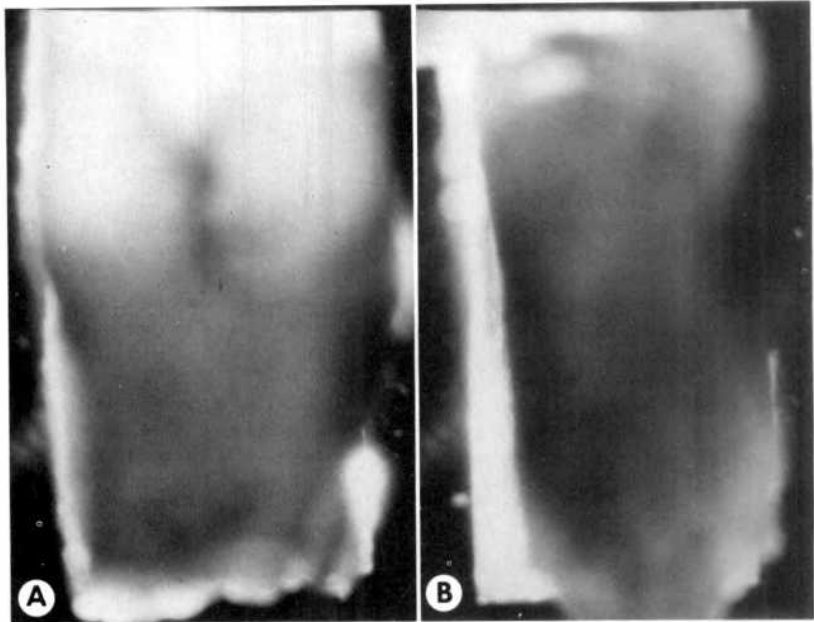


Fig 1. Artist's depiction of soft palate specimen as viewed from above, anterior, and right side. Intersecting planes depict planes of histologic sections. Coronal plane is 3 mm posterior to cut nasal mucoperiosteum, superiorly adjacent to edge of hard palate. Thickness of soft palate specimen was measured at intersection of coronal and midsagittal planes.

Fig 2. Photomacrographs of infrared transillumination of two soft palates. Orientation of specimens is such that edge attaching to hard palate is at top of picture. Areas that appear white had more light showing through. Both of these images were consistently categorized as having moderate overall intensity. A) Has midline band of opaqueness, which was associated with increased midline muscle tissue. B) Lacks midline opaque band.



tive to wavelengths as long as about 900 nm. Wavelengths shorter than about 740 nm were not transmitted by the Kodak No. 87 filter. After establishing exposure parameters by trial and error, we used identical exposure parameters for the 35 specimens. The specimens, which were stored at room temperature, were photographed the same day, onto one roll of film, and printed onto one contact sheet. One of us (B.L.K.) twice categorized the images as to overall appearance (white, gray, or black — ie, translucent, partially translucent, or opaque to the infrared wavelengths) and whether or not the photograph demonstrated a midline longitudinal band of decreased infrared transmission (Fig 2). Images sorted inconsistently were excluded from data analysis.

Histologic Examination. Two histologic sections were studied for each palate specimen: midsagittal and coronal (Fig 1). The 70 sections were fixed in formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and mounted on slides. As planned, assessments were done of the fibers of the musculus levator veli palatini, dorsal midsagittal muscle fibers (musculus uvulae), and midsagittal fibrous tissue. Some other histologic features obviously varied, and these were assessed too: ventral midsagittal muscle fibers (presumably representing the musculus palatoglossus) and the amount of salivary gland tissue (Table 1 and Fig 3). Only categorizations (done by B.L.K.) that were consistent were used for data analysis.

STATISTICAL METHODS

The statistical unit was the head specimen. Scatterplots were studied, and data of apparent nonrandom patterns were assessed statistically. The Fisher exact test was used to compare proportions. The rank sum test was used to compare the distributions of two groups. To reject a null hypothesis (of no association, or that the distributions of two groups

are the same), the p (two-tailed) value is stated. Although multiple (54) comparisons were done, the given p values are not modified by any sort of Bonferroni correction.

RESULTS

The histologic features were easily identifiable (Fig 3). The repeatability of most characterizations was excellent (Table 1). There were some interesting associations among the soft palate parameters. A paucity of fibers of the musculus uvulae was associated with poor organization of the fibers of the musculus levator veli palatini ($p < .005$, $N = 25$; Table 2). For example, of the 15 specimens with a musculus uvulae that was macroscopically obvious, none had a haphazard array of the musculus levator veli palatini. Surprisingly, a haphazard arrangement of fibers of the musculus levator veli palatini was associated with increased palatal thickness (measured 3 mm from the edge of the hard palate; $p = .005$, $N = 33$). The thicker palates tended to not have identifiable fibers of the musculus palatoglossus ($p < .005$, $N = 25$).

The overall amount of infrared transillumination seemed related to specimen thickness, ie, the thinner specimens tended to be more lucent. The midline palatal opaqueness to infrared tended to occur in specimens having an abundance of the musculus uvulae. No relationship of sex or salivary gland amount was suggested with any palate parameter or otitis indicator.

Minuscule submucous cleft palate seemed to trend with indicators of prior otitis media; however, no statistical relationship was found (Fig 4). A large number of fibers of the musculus uvulae tended to be more common in cadavers having healthy ears. Surprisingly, the cadavers having comparatively thin soft palates, as measured in the midline 3 mm

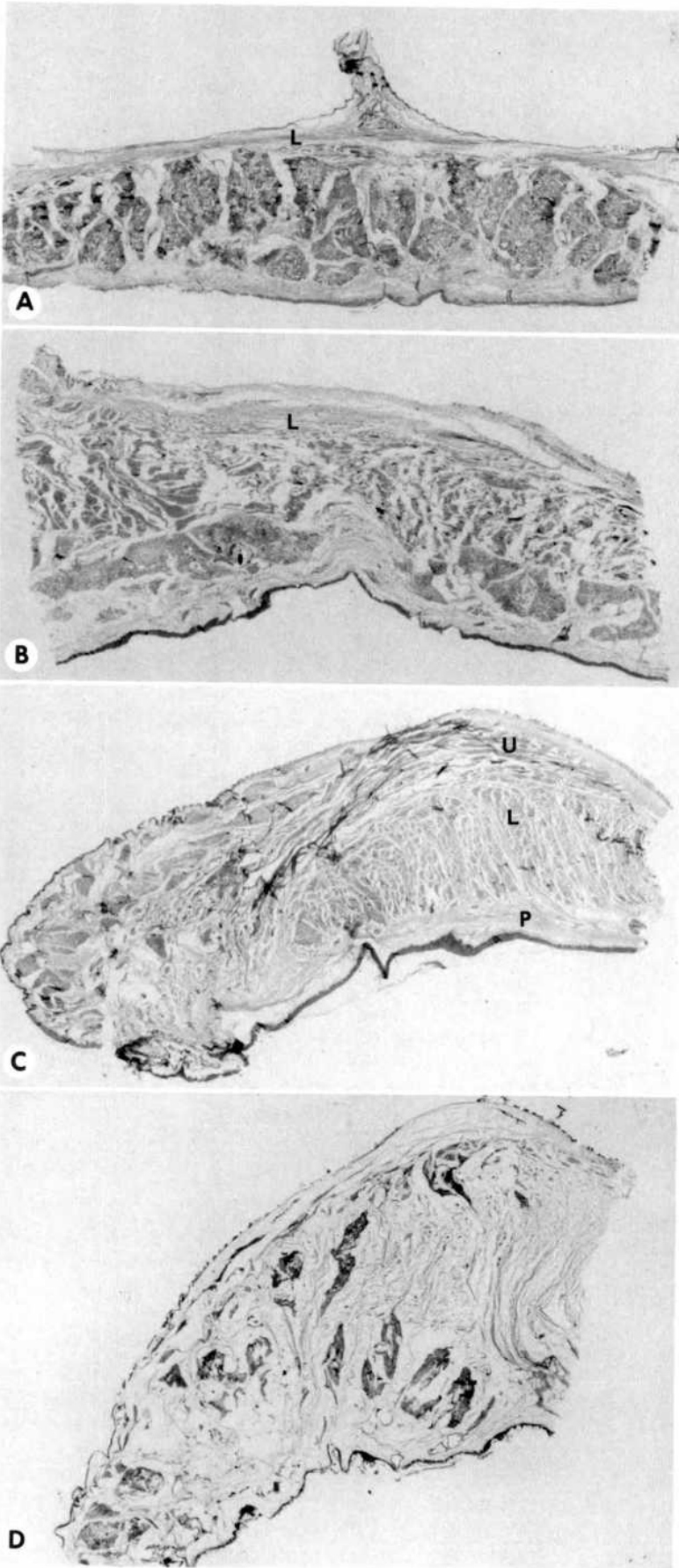


Fig 3. Photomicrographs of histologic sections. A) Low-power, coronal. Exhibits negligible midline fibrosis, organized (but few) fibers of musculus levator veli palatini (L), and abundant salivary glands. Compare with B. B) Another specimen's coronal section. Note midline fibrosis, organized fibers of musculus levator veli palatini (L), and few salivary glands. Compare with A. C) Low-power, midsagittal. Exhibits organized fibers of musculus levator veli palatini (L), prominent fibers of musculus uvulae (U), and some fibers of musculus palatoglossus (P). Contrast with D. D) Another specimen's midsagittal section. Note haphazard array of fibers of musculus levator veli palatini, few fibers of musculus uvulae, absence of fibers of musculus palatoglossus, and predominance of loose connective tissue. Contrast with C.

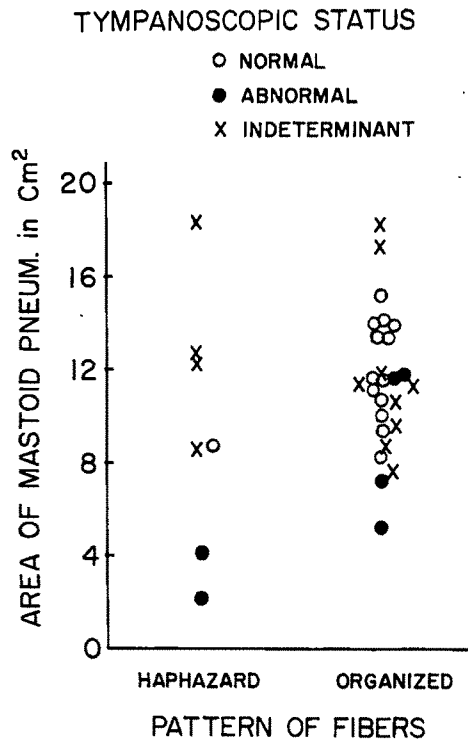


Fig 4. Scatterplot showing that specimens having haphazard array of fibers of musculus levator veli palatini tended to have indicators of prior otitis media (small mastoid pneumatization and scarred tympanic membranes). Both specimens not included in this scatterplot had inconsistently categorized musculus levator veli palatini. Both heads were considered tympanoscopically normal; mean areas of mastoid pneumatization were 6.1 and 13.7 cm².

from the hard palate, tended to have healthy ears.

DISCUSSION

There was only a trend of minuscule submucous cleft palate being associated with indicators of prior otitis media. In addition to the obvious explanation that no true association exists, additional explanations may be offered.

1. The specimens were comparatively healthy as regards the middle ear. Although some had evidence of prior otitis media, on the average, the extent of mastoid pneumatization was slightly larger (12%) than that defined as "normal" by Diamant's classic work.¹⁶

2. We chose inappropriate soft palate parameters. Perhaps by placing the coronal histologic section adjacent to the edge of the hard palate, there would have been a better study of the abnormal insertion by the musculus levator veli palatini. Possibly the midsagittal histologic section did not sufficiently include fibers of the musculus uvulae. The musculus uvulae is a paired muscle, its two bellies separated by a variable amount of fibrous tissue.¹⁹ However, the typical fibrous septum is so narrow (see Fig 4 of Azzam and Kuehn¹⁹) that a perfect midsagittal histologic section, avoiding all fibers of the musculus uvulae, could be made only rarely.

TABLE 2. RELATIONSHIP OF ARRAY OF FIBERS OF MUSCULUS LEVATOR VELI PALATINI TO EXTENT OF MUSCULUS UVULAE

Fibers of Musculus Uvulae	Organization of Fibers of Musculus Levator Palatini	
	Haphazard	Organized
Obvious macroscopically	0	15
Few macroscopically	1	6
Seen microscopically	1	0
No fibers	2	0

Association of abundant fibers of musculus uvulae with organized pattern of musculus levator veli palatini is unlikely by chance ($p < .005$). Omitted from this Table are 10 specimens with inconsistent categorizations of musculus uvulae; 2 of these 10 specimens were also inconsistently categorized as to musculus levator veli palatini.

Therefore, we think the midsagittal histologic technique cannot explain the nearly 20% occurrence of hypoplasia of the musculus uvulae.

The histologic data of this study are consistent with the findings of Altermatt et al²⁰ and Kuehn and Kahane.²¹ From this foundation, our data address the interrelationship of the bases for nasopharyngoscopic and surgical dissection criteria used to identify occult submucous cleft palate. Nasopharyngoscopists report "V-shaped midline defects on the nasal surface of the velum"^{12(p150)} or reduced bulk of the musculus uvulae to account for a decreased bulge or abnormal morphology of the dorsum of the soft palate.²² The surgical dissection criteria include abnormal orientation and deficiency of the musculus levator veli palatini.^{7,8} Neither Kaplan⁷ nor Trier⁸ describes an abnormality of the musculus uvulae. None of the authors using nasopharyngoscopy have validated the absence of a uvular muscle by histologic study or surgical exploration.⁸ That is, the nasopharyngoscopists can be criticized for having neither histologic nor surgical dissection evidence of a small abnormal musculus uvulae in their label of occult submucous cleft palate. The surgical dissectors can be criticized for not having data on normal vela.

Our histologic data suggest that the midsagittal paucity of the musculus uvulae directly relates to a haphazard array (in both midsagittal and coronal sections) of the musculus levator veli palatini (Table 2). These data from clinically normal palates may be interpreted to support the nasopharyngoscopic inference that in occult submucous cleft palate, there is hypoplasia of the musculus uvulae or "some degree of diastasis of the remaining palatal musculature."^{13(p590)}

The trend suggesting a correlation of indicators of prior otitis media with increased palatal thickness, measured 3 mm posterior to the edge of the hard palate, is intriguing. This is especially so when one considers the statistically significant relationship of palatal thickness and haphazard pattern of the musculus levator veli palatini. This finding is the inverse of what had been expected, and seems inconsistent with the dorsal longitudinal V-shaped

defect used by Croft et al.¹² to endoscopically identify occult submucous cleft palate. However, we doubt that in vivo thinness would artifactually manifest as postmortem thickness. We suspect that occult submucous cleft palate specimens are relatively thick near the hard palate, where we measured palate thickness, which is also where Kaplan⁷ and Trier⁸ find abnormal insertion of the musculus levator veli palatini. We suspect that further posterior, where Croft et al.,¹² Lewin et al.,¹³ Shprintzen et al.,⁹ and Velasco et al.²² describe the abnormal morphology of the dorsal velum, the soft palate is thinner than normal. If our suggestion is substantiated, then infrared transillumination of the posteri-

or velum may be useful in identifying hypoplasia of the musculus uvulae.

In summary, in a study of 35 clinically normal soft palates, we found about one fifth to have a minuscle submucous cleft palate. We suspect that some of the minuscle clefts could have been recognized by surgical dissection.^{7,8} The minuscle clefts, in addition to having a haphazardly organized musculus levator veli palatini and hypoplasia of the musculus uvulae, lacked midline fibers of the musculus palatoglossus and were relatively thick anteriorly. A trend was suggested for minuscle clefts to be associated with indicators of prior otitis media.

ACKNOWLEDGMENTS — R. L. Blakely, PhD, used physical anthropology criteria to categorize the specimens as to sex. R. L. Maresca, MD, categorized the tympanic membrane photographs. K. J. Winn, MD, and S. Fox did the histologic preparations. D. Cerenko, MD, translated the article of Altermatt et al.²⁰

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ANIMAL MODEL FOR ISCHEMIC FACIAL NERVE PARALYSIS WITH SELECTIVE VASCULAR EMBOLIZATION

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An experimental model that reliably and easily produces acute ischemic facial nerve paralysis would be useful for the controlled study of treatment and to improve our understanding of the pathophysiology and treatment of facial nerve palsy. Most documented models that simulate clinical facial nerve palsy cause direct damage to the nerve. We describe an experimental model for ischemic facial nerve paralysis in the cat that employs arterial block of the internal and external maxillary and posterior auricular arteries using embolizing material (Avitene). All animals develop stable acute ischemic facial nerve palsy lasting for approximately 2 months. Electromyographic study of this model revealed that the site of the lesion resulting from selective embolization may be within the temporal bone. This model has the advantages of simplicity of technique, cost-effective use of cats, and reproducibility of facial nerve palsy.

KEY WORDS — animal model, facial nerve, ischemic facial nerve palsy, selective embolization.

Facial nerve paralysis is a widespread and disturbing clinical facial nerve disorder that has been the focus of increasing attention during recent decades. Previous studies include investigation of its cause, diagnosis, and treatment. It is discouraging that the precise cause, pathogenesis, and pathophysiology of facial nerve paralysis have not been resolved. There are two major concepts regarding the pathophysiology and etiology of idiopathic Bell's palsy. In the past, most authors accepted the old general theory of a vicious cycle of edema and compressive ischemia affecting the facial nerve within its bony canal.^{1,2} The recent entrapment neuropathy theory³ postulates that edema of the facial nerve in the meatal foramen causes nerve constriction at this point. The other concept that cannot be ignored is that of viral infection as a cause of acute peripheral facial paralysis.^{4,5}

In the absence of a suitable animal model for ischemic or viral facial paralysis, most previous reports have been of human studies, which are restricted by the limitations of human investigation. Models of human ischemic or viral facial nerve paralysis in animals, whether naturally occurring or experimentally induced, may offer a great opportunity to analyze the pathogenic mechanisms and provide a major breakthrough in the field of facial nerve research and also in the development and evaluation of treatment that would not be possible to perform experimentally in humans.

There are, however, only a few references in the literature on experimental research on the cause of Bell's palsy. The pioneers in experimental facial nerve research were McGovern et al,⁶⁻⁸ who performed studies on ischemic facial paralysis in which

predictable facial paralysis was produced by injecting a vasoconstrictor agent into the canal. They concluded that the mechanism of the paralysis appeared to be ischemic, and their results added evidence to support the ischemic hypothesis of Bell's palsy. In a similar fashion, Ogawa et al⁹ injected epinephrine into the stylomastoid foramen of guinea pigs; this procedure resulted in facial weakness of short duration only. The other route to experimental facial nerve palsy is by direct approach to the nerve, such as circumferential compression of the exposed facial nerve of cats¹⁰ or application of ice to the shaven face of rats¹¹ or to the mastoid region of rabbits,¹² but it is probable that these approaches do not establish a good animal model for facial nerve palsy.

In this study, we therefore attempted to create an animal model of peripheral facial paralysis by applying a selective embolization technique to induce conduction block of the facial nerve, and also 1) to test what type of selective embolization would be the most effective and 2) to ascertain whether ischemic facial nerve degeneration would ensue.

ANATOMIC CONSIDERATIONS

In humans, the blood supply to the facial nerve is from the stylomastoid artery, a branch of the posterior auricular artery; from the petrosal branch of the middle meningeal artery, a branch of the internal maxillary artery; and from the internal acoustic artery.¹³⁻¹⁵

Recently, Balkany¹⁶ demonstrated the detailed intrinsic vasculature of the cat facial nerve, and also described the extrinsic circulation. The main blood supply to the facial nerve in cats,¹⁶ as in humans, is

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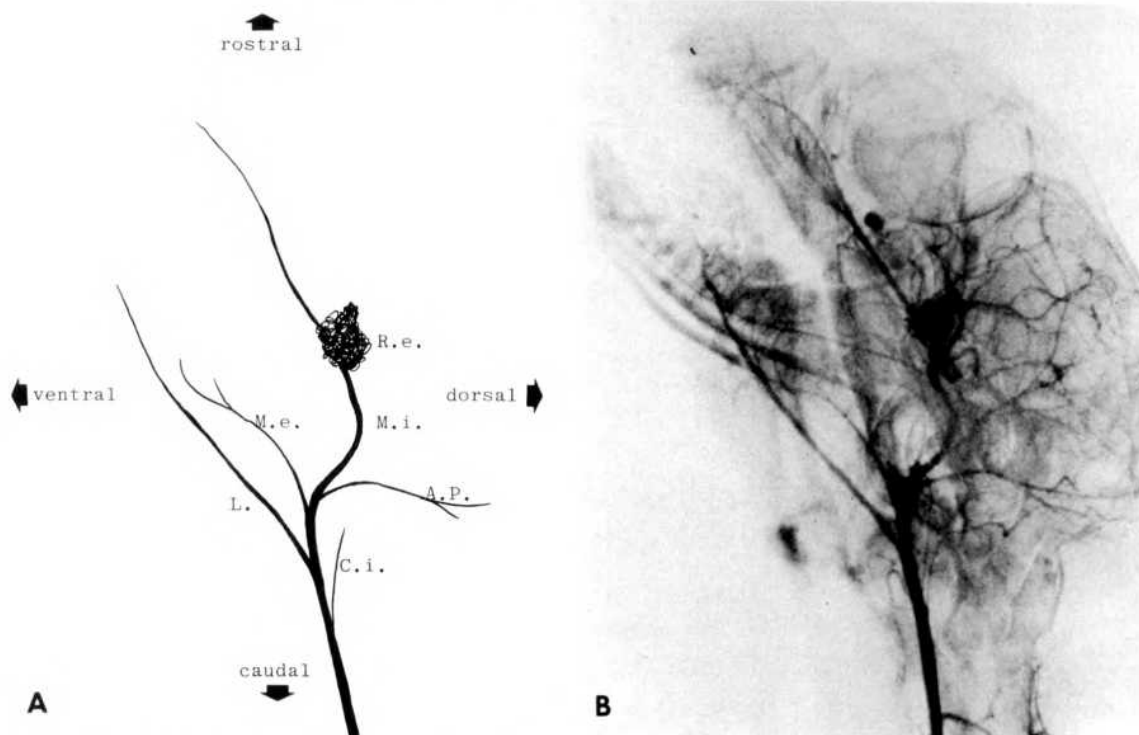


Fig 1. Subtraction carotid angiogram of head area including temporal bone. There is S-shaped curve in internal maxillary artery proximal to external rete. A) Schematic illustration. R.e. — external rete (carotid plexus), M.i. — internal maxillary artery, M.e. — external maxillary artery, L. — lingual artery, A.P. — posterior auricular artery, C.i. — internal carotid artery. B) Actual angiogram.

from the anterior inferior cerebellar artery; the petrosal artery, a branch of the middle meningeal artery; and the stylomastoid artery, a branch of the posterior auricular artery. The cranial auricular branch of the posterior auricular artery supplies the mastoid area. The other important blood supply to the extrinsic circulation is a branch from the anastomotic plexus of the stylomastoid and petrosal vessels. The distal branch of the petrosal artery anastomoses with the stylomastoid artery adjacent to the vertical segment of the facial nerve, and the proximal branch runs across the horizontal segment of the facial nerve.

In the labyrinthine segment, the facial nerve receives branches directly from the anterior inferior cerebellar artery, internal auditory artery, and internal carotid artery. The geniculate ganglion is not as prominent as it is in humans, although there is a large vascular supply in the nerve sheath surrounding the geniculate ganglion, in which the internal auditory artery anastomoses with a branch of the petrosal artery.

A subtraction angiogram of the cat temporal bone area and a schematic illustration are shown in Fig 1. The S-shaped curve in the internal maxillary artery, the posterior auricular artery, a very tiny internal carotid artery, and the external rete (carotid plexus) are clearly demonstrated.

MATERIALS AND METHODS

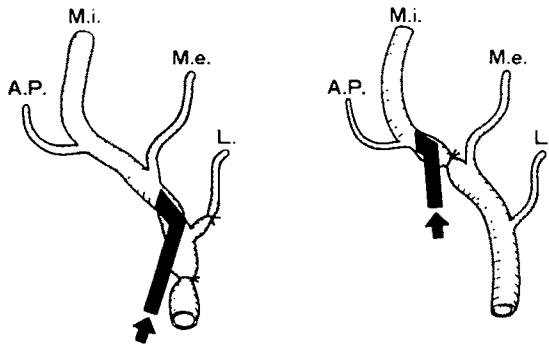
According to these anatomic considerations, se-

lective embolization of the main vessels supplying the facial nerve in the temporal bone of the cat, stylomastoid artery, and middle meningeal artery was performed.

Healthy adult cats of both sexes weighing more than 2.5 kg were used. During the experimental procedures and measurements, complete anesthesia was achieved with ketamine hydrochloride (0.5 g/10 mL) administered by intraperitoneal injection at a dose of 40 mg/kg. All experimental procedures were performed on the right side of each cat, with the untreated left side in the same animal serving as the control. Four types of embolization were attempted with Avitene (microfibril bovine collagen, Alcon Inc, Humacao, Puerto Rico) in different concentrations. The four types of embolization are schematically illustrated in Fig 2. With type 1 embolization, the external maxillary, internal maxillary, and posterior auricular arteries are occluded; with type 2 embolization, the internal maxillary and posterior auricular arteries are occluded; with type 3 embolization, only the internal maxillary artery is occluded; and with type 4 embolization, only the posterior auricular artery is occluded. A fine catheter of 1.0 mm diameter is used (Fig 2).

In an acute preparation to record the evoked electromyographic (EMG) response of the orbicularis oris muscle, direct stimulation of the contralateral motor cortex or extratemporal facial nerve was applied. The blink or corneal reflex was also ex-

Type 1 embolization Type 2 embolization



Type 3 embolization Type 4 embolization

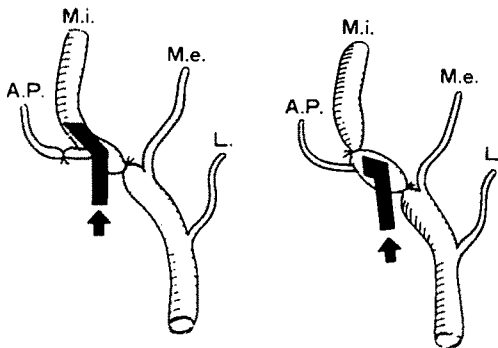


Fig 2. Schematic illustration of four types of selective embolization used in study. Abbreviations as in Fig 1.

amed as a simple method of detection of the onset of facial nerve paralysis. These animals underwent tracheostomy and insertion of an intravenous line. Their respiratory status was maintained with a Harvard ventilator.

Prior to measurement of the evoked EMG response to peripheral facial nerve stimulation, the extratemporal facial nerve was exposed in the right parotid gland region. A bipolar silver-silver chloride electrode was placed over the motor cortex in the frontal area. The usual direct motor cortex stimulation was 5- to 15-mA current with a duration of

0.1 to 0.3 milliseconds delivered as a single pulse.

RESULTS

Correlation of Different Types of Embolization and Facial Nerve Paralysis. The rate of induction of facial nerve paralysis by each of the four different types of embolization was correlated with the concentration and volume of Avitene suspension, as shown in the Table. With type 1 embolization, complete paralysis occurred in 26 of 30 cats (87%), with type 2 embolization it occurred in 23 of 24 cats (96%), with type 3 in 1 of 2 cats (50%), and with type 4 in 2 of 4 cats (50%). The time required for complete facial nerve paralysis to develop was 20 to 30 minutes (mean, 20 minutes) for type 1 embolization, 15 to 110 minutes (mean, 29 minutes) for type 2, 35 minutes for type 3, and 20 to 30 minutes for type 4.

These findings strongly suggest that a concentration of Avitene's suspension greater than 1.0% and a volume greater than 1.5 to 2.0 mL is sufficient to cause facial nerve paralysis with embolization types 1 and 2.

In all animals studied, neither facial gangrene nor cranial nerve deficit other than that of the facial nerve developed. Forty to 60 days after embolization, complete facial nerve function had returned in most (nearly 90%) of the experimental animals that developed complete facial paralysis.

Electromyography of Orbicularis Oris Muscle. Motor-evoked potentials of the orbicularis oris muscle by direct stimulation of the motor cortex were monitored throughout the experimental period in five animals in each group of type 1 and type 2 embolization as an acute preparation.

A representative evoked EMG response to direct stimulation of the contralateral (left) motor cortex before and after type 2 embolization (2.0 mL of 1.0% Avitene) recorded from cat 31 is shown in Fig 3. Prior to embolization, stimulation elicited evoked muscle potentials in the right orbicularis oris muscle

DEGREE OF FACIAL NERVE PALSY RESULTING FROM DIFFERENT TYPES OF EMBOLIZATION USING DIFFERENT VOLUMES AND CONCENTRATIONS OF AVITENE

Type of Embolization	Concentration of Avitene (%)	Volume of Avitene (mL)	Facial Nerve Paralysis (No. of Animals)		
			Complete	Incomplete	Absent
1	0.25	2.5			1/1
		2.5	1/2		1/2
		<1.5		1/2	1/2
	2.0	≥1.5	23/23		
		<1.5	1/1		
		>1.5	1/1		
	Total		26/30	1/30	3/30
2	0.75	3.0	3/4	1/4	
	1.0	0.5	1/1		
		>1.5	19/19		
	Total		23/24	1/24	0/24
3	1.0	>1.0	1/2	1/2	
4	1.0	>2.0	2/4	1/4	1/4

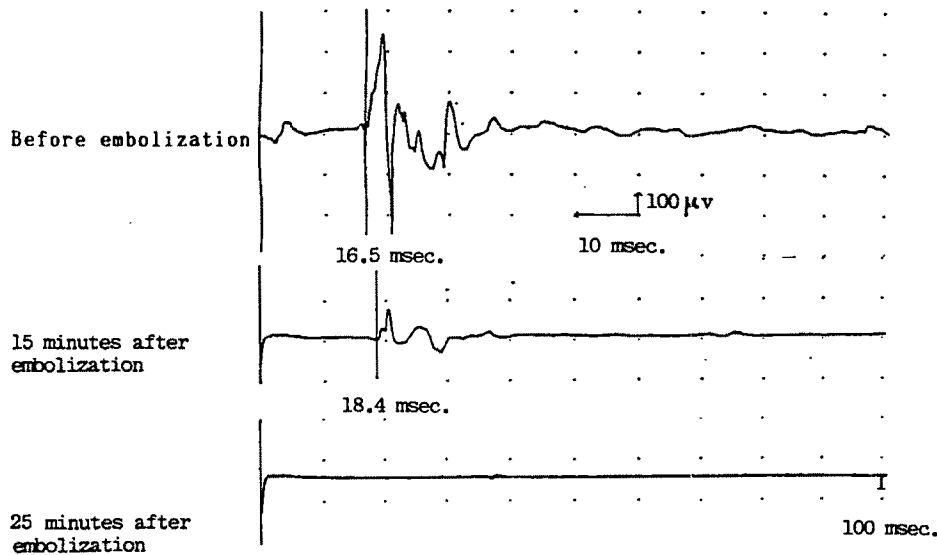


Fig 3. Evoked electromyographic responses of orbicularis oris muscle on side of embolization with direct stimulation (single pulse) of contralateral motor cortex (cat 31, type 2 embolization).

with a latency of 16.5 milliseconds. Fifteen minutes after embolization, the evoked muscle response was delayed, with a latency of 18.4 milliseconds, and showed a marked decrease in amplitude. Twenty-five minutes after embolization, no evoked EMG response could be elicited, and no blink reflex was observed with the air-blowing test. To verify that the conductivity of the extratemporal portion of the facial nerve on the completely paralyzed side was not affected by the embolization, the evoked EMG response of the orbicularis oris muscle to stimulation of the extratemporal facial nerve was recorded in cat 35 after type 2 embolization (2.0 mL of 1.0% Avitene). After the presence of complete facial nerve paralysis was confirmed, the animal was carefully returned to its cage in a stable condition with sufficient medication. The results obtained from this animal 24 and 48 hours after embolization are shown in Fig 4. The evoked EMG response to stimulation of the extratemporal facial nerve of the

nonparalyzed left side was compared to that of the paralyzed right side.

The upper trace in Fig 4 shows no apparent change 24 hours after embolization; however, the lower trace shows a marked decrease in amplitude of the evoked EMG 48 hours after embolization, suggesting that degeneration of the facial nerve developed beyond the temporal bone portion of the paralyzed side.

Histopathology of Temporal Bone. Photomicrographs of the control side and paralyzed side of the facial nerve in the cat temporal bone are shown in Fig 5, which demonstrates an occluded vessel in the paralyzed side without any changes in the number or orientation of axons 24 hours after embolization. Figure 6 shows a photomicrograph of the horizontal segment of the affected facial nerve demonstrating decreased numbers and loss of orientation of axons 48 hours after embolization.

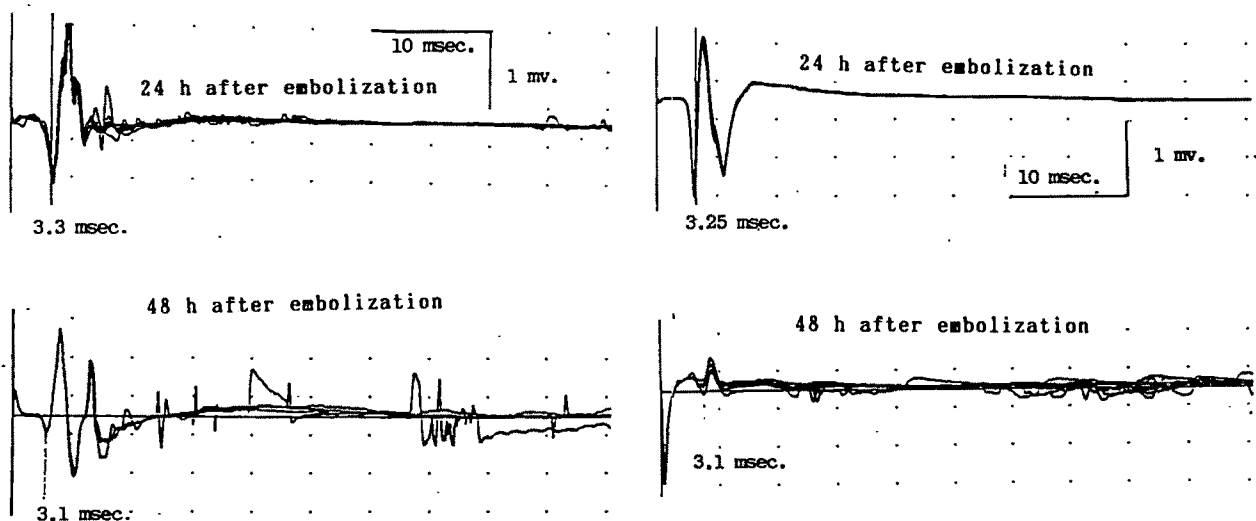


Fig 4. Evoked electromyographic response of orbicularis oris muscle of paralyzed side with direct stimulation of extratemporal portion of facial nerve after establishing complete facial nerve paralysis (cat 35, type 2 embolization). Left side of figure — non-paralyzed side, right side of figure — paralyzed side.

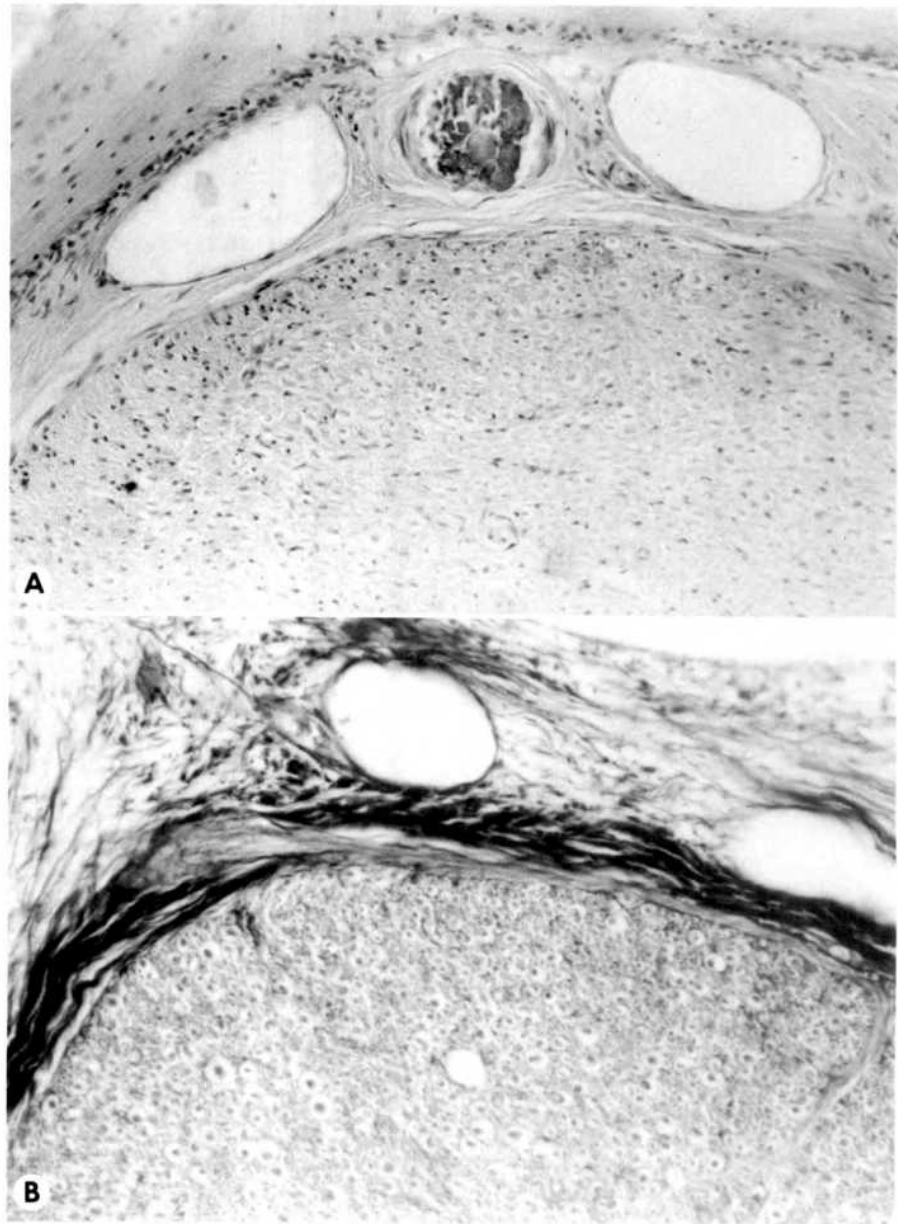


Fig 5. Histopathology of vertical portion of facial nerve 24 hours after development of complete facial nerve paralysis (original x100). A) Paralyzed side. B) Nonparalyzed side. There is no significant decrease in number of axons or orientation of axons. Embolus is present in vessel on paralyzed side.

DISCUSSION

The ischemic facial nerve paralysis model was developed as a result of clinical experience. Calcuterra et al¹⁷ in 1976 first described two patients undergoing embolization of vascular intracranial tumors who developed total peripheral facial paralysis that persisted for at least 6 months after occlusion of the middle meningeal artery. They stated that although no general conclusions can be drawn from observations made in only two patients, attention should be directed toward the role of primary ischemia of the petrosal branch of the middle meningeal artery as a possible causal factor in idiopathic facial nerve paralysis. Following this report, experiments were performed with the objective of developing an animal model for ischemic facial nerve paralysis. A review of the literature on facial nerve paralysis after embolization of the ex-

ternal carotid artery was published in 1986.¹⁸

In our present experimental series, attempted embolization of the middle meningeal artery (branch of the internal maxillary artery) and posterior auricular artery with Avitene resulted in a higher incidence of complete facial paralysis without development of facial gangrene or other cranial nerve deficit compared to previous models, such as instilling vasoconstricting drugs into the fallopian canal of dogs.⁸ These results suggest that ischemia developed in both 1) the geniculate ganglion and the horizontal portion of the facial nerve supplied by the petrosal branch of the middle meningeal artery and 2) the descending portion of the nerve supplied by the stylomastoid artery.

An important finding of our study concerns the site of conduction block in the facial nerve and its

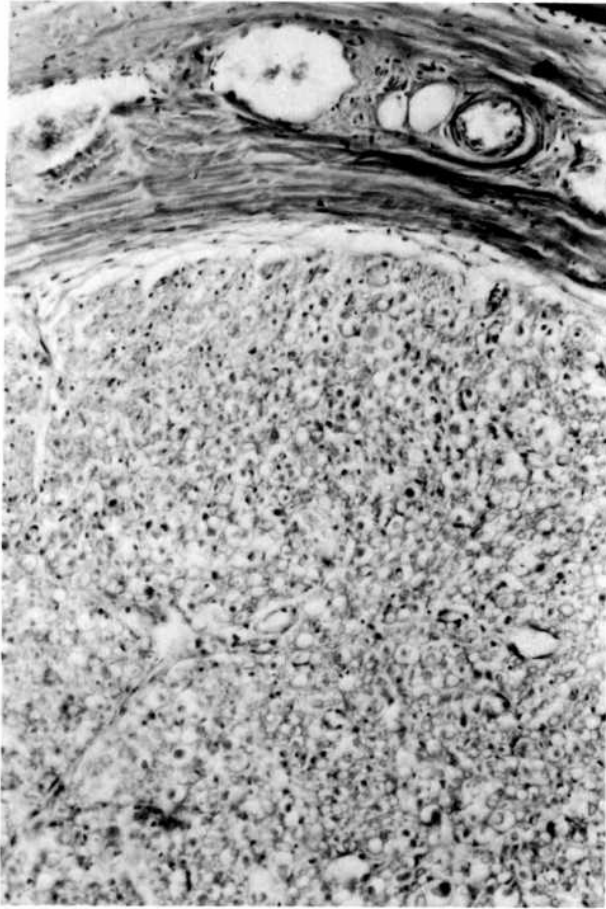


Fig 6. Histopathology of horizontal portion of facial nerve 48 hours after development of complete facial nerve paralysis demonstrates decrease in number and orientation of axons (original x100).

ischemic nerve fiber degeneration. When the facial motor cortex is activated, the resulting motor signal, the motor-evoked potential, is recorded traveling down the pons, finally activating muscle potentials. In the present study, the motor-evoked potential was completely abolished within the temporal bone portion of the facial nerve (precise neurophysiologic data will soon be reported in a future paper); this finding indicates that the site of the lesion of facial nerve paralysis was within the tempo-

ral bone.

The pathologic changes of degeneration in ischemic facial nerve fibers were clearly demonstrated 48 hours after embolization, and degeneration was confirmed by EMG recordings of the orbicularis muscle when the extratemporal portion of the facial nerve was stimulated. After ischemic facial nerve damage, experimental animals showed recovery of paralysis 40 to 60 days after embolization, and histopathologic examination of the facial nerve revealed that axonal regeneration of the nerve was coincident with the reestablishment of vascular flow. (These findings will be separately reported in detail.)

In terms of the clinical picture of facial nerve paralysis, the availability of an animal model of acute facial paralysis that is analogous to the human condition may expedite not only the study of facial nerve paralysis but also its treatment, such as with steroid therapy, by providing a basis for standardization of results. In addition, during the early stage of established facial nerve paralysis, the state of neurapraxia or axonotmesis that occurs in Bell's palsy can be reproduced in animals. Therefore, the present study provides a further basis for research by which investigators can predict facial nerve recovery or the prognosis of patients with facial nerve paralysis by using some simple outpatient techniques such as a nerve excitability test or evoked EMG.

Our model resulted in an arterial block and a relatively chronic state of paralysis that reliably developed within an hour. Its advantages over previously reported models include the occurrence of reproducible facial nerve paralysis in almost all animals. We are encouraged by the consistency of our results in developing an animal model for the study of facial nerve paralysis, and are currently conducting neurophysiologic and histologic examinations of the paralyzed nerves. We believe that both our animal model and the animal model of viral facial palsy reported by Ishii et al¹⁹ in 1990 represent vital steps toward future facial nerve research.

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MALFORMATION AND DEGENERATION IN THE INNER EAR OF MOS TRANSGENIC MICE

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Transgenic mice carrying the *mos* proto-oncogene linked to a retroviral transcriptional control sequence display behavioral abnormalities including circling, hyperactivity, head tilt, and bobbing. Axonal degeneration, neuronal chromatolysis, spongiform encephalopathy, gliosis, and inflammatory infiltrates are reportedly found in the central nervous systems of all mutants with the behavioral traits. Hearing was tested by means of broadband free-field rarefaction clicks with auditory brain stem response recorded between vertex and mouth electrodes. No detectable auditory response was elicited in transgenic animals, in contrast to five distinct positive peaks observed in littermate control animals. Light microscopic survey of temporal bone histopathology in mutants revealed extensive degeneration of the organ of Corti with loss of hair cells in all cochlear turns and loss of supporting cells and atrophy of spiral ganglion cells. The spiral limbus was deformed, with replacement of the usual convexity of the superior surface by a flattened trough configuration. Hair cells of the vestibular end organs appeared normal. Pathologic alteration in levels of *mos* transgene RNA appears to have a direct effect on the structural integrity of the inner ear.

KEY WORDS — inner ear, mouse deafness, transgenic mutant.

INTRODUCTION

By means of a pronuclear injection technique, seven lines of mice have been created that stably integrate and transmit the *mos* gene linked to a retroviral transcriptional control sequence.¹ These lines exhibit variable behavioral abnormalities that are all reminiscent of the many well-known circling mutants in the mouse. The *mos* animals display head tossing, head tilt, hyperactivity, circling, and deafness. Expressivity in heterozygotes and homozygotes is variable and the age at onset of phenotypic expression varies as well. Circling behaviors in mutant mice are generally attributed to malformation or degeneration of the inner ear. In order to determine if *mos* transgenic mutants have inner ear abnormalities, we performed tests of hearing using brain stem auditory evoked potential (BAEP) measurements and surveyed the temporal bones by light microscopy in the MOS-3 strain, which was derived by pronuclear injection into fertilized eggs from FVB/N mice.^{1,2}

MATERIAL AND METHODS

Animals. Transgenic mice and normal littermate controls were bred directly from lines created by Khillan et al.² Briefly, founder mice of the three original *mos* transgenic lines were derived from one-cell embryos of the inbred strain FVB/N by microinjection of pTS74 plasmid sequences either linearized with *SalI* or excised as an *EcoRI-SalI* fragment. One of the founders was female and the other two were male. All three transmitted the genetic trait to progeny. Southern blot analysis of genomic DNA from progeny of the three lines re-

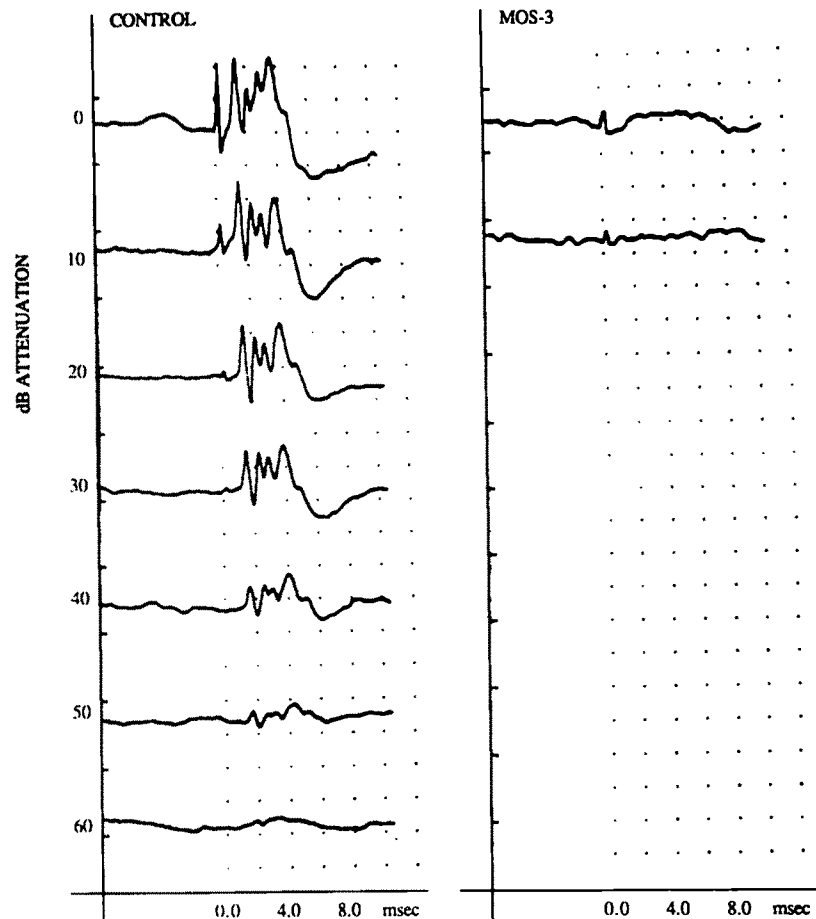
vealed unique patterns for each line, suggesting independent sites of integration. Using the bands of endogenous *mos* sequences as a reference, Khillan et al determined that the first line (MOS-1) contained one copy and lines 2 and 3 (MOS-2 and MOS-3, respectively) contained three to four copies of the transgene per haploid genome.² The MOS-3 line was used for this study.

Electrophysiology. The hearing thresholds of young transgenic mice from 2 to 12 weeks of age and littermate controls were determined by evoked response audiometry. Animals were anesthetized with either intraperitoneal Avertin 0.02 mL/g body weight or intramuscular ketamine hydrochloride 0.2 mg/g body weight and positioned on a temperature-controlled testing platform in an electrically shielded, sound-attenuating booth. Free-field rarefaction clicks generated by 30-microsecond electrical pulses at a rate of 30/s were delivered by a Sennheiser HD424 earphone (1 to 20 kHz nominal bandwidth) positioned 8 cm in front of the snout. Potentials were recorded differentially between a positive pin electrode at the vertex and a negative electrode mouth bar against the palate. The potentials were sampled at 80-microsecond intervals and averaged over a 20-millisecond interval beginning 8 milliseconds before each click. The recording bandwidth was 270 to 1,300 Hz. A threshold for detection of evoked potential activity was determined for each animal by means of a standardized setup in which the 120-dB signal was attenuated in 5- or 10-dB increments until visual comparison failed to detect any difference between prestimulus and poststimulus activity, thresholds being defined as the most at-

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Fig 1. Brain stem auditory evoked potential (BAEP) audiometry. Control animals (left panel) exhibit five distinct positive peaks that decline in amplitude with progressive attenuation of stimulus intensity. MOS-3 BAEP (right panel) shows no response, even at maximal stimulus intensity. Small peak at 0.0 milliseconds is signal artifact.



tenuated stimulus level at which the waveform was still visible. Control animals consistently demonstrated threshold at 60 dB attenuation.

Temporal Bone Pathology. Animals for temporal bone study were deeply anesthetized by intraperitoneal Nembutal and fixed by intracardiac perfusion with 10 mL heparinized saline followed by 12 mL Heidenhain Susa fixative. All soft tissue was debrided from the skulls, which were then post-fixed, decalcified in trichloroacetic acid, and embedded in celloidin. Tissue blocks were serially sectioned at 20 μ m and every fifth section was stained with hematoxylin and eosin and mounted.

RESULTS

Electrophysiology. Control animals ($n = 6$) all exhibited typical BAEP findings of five distinct positive peaks observable at high stimulus intensity and gradual loss of visual detection of waveforms with progressive attenuation of stimulus intensity such that threshold for visual detection was noted at 50 to 60 dB attenuation of the standard signal (Fig 1). The BAEP recordings from all MOS-3 mutants ($n = 5$) revealed total absence of any BAEP waveform, even at full stimulus intensity (Fig 1).

Temporal Bone Pathology. Specimens for histopathologic study were whole heads serially sec-

tioned, providing opportunity to note central nervous system involvement by the expression of the *mos* transgene. All MOS-3 animals exhibited spongiform lesions scattered throughout the brain stem and cerebellum, including the cochlear nucleus and cochleovestibular nerve in some cases. The bony otic capsule showed no abnormalities of general shape or size, and middle ear structures appeared normal as well. Reissner's membrane was normal and no instances of endolymphatic hydrops were noted. The osseous spiral lamina, spiral ligament, and stria vascularis were all normal as well.

Cochlear abnormalities were confined to the spiral limbus, organ of Corti, and spiral ganglion cells. There was prominent deformity of the spiral limbus throughout the entire cochlea in all mutant ears. The convex surface of the spiral limbus, normally apposed to the attachment of Reissner's membrane, exhibited a deep trough with flattening of the normal convexity and loss of the normal palisade of interdental cells (Fig 2). The stellate supporting cells of the central portion of the spiral limbus were normal. There were flattened cells with dark nuclei lining the trough that may represent degenerated or deformed interdental cells. The tectorial membrane was detached from the organ of Corti and somewhat contracted but otherwise appeared grossly normal. Profound degeneration of the organ



Fig 2. Twenty-micron sections of mouse organ of Corti (H & E). A) Low-power view of normal specimen (original $\times 100$). B) High-power view of same specimen (original $\times 200$). (Continued on next page.)

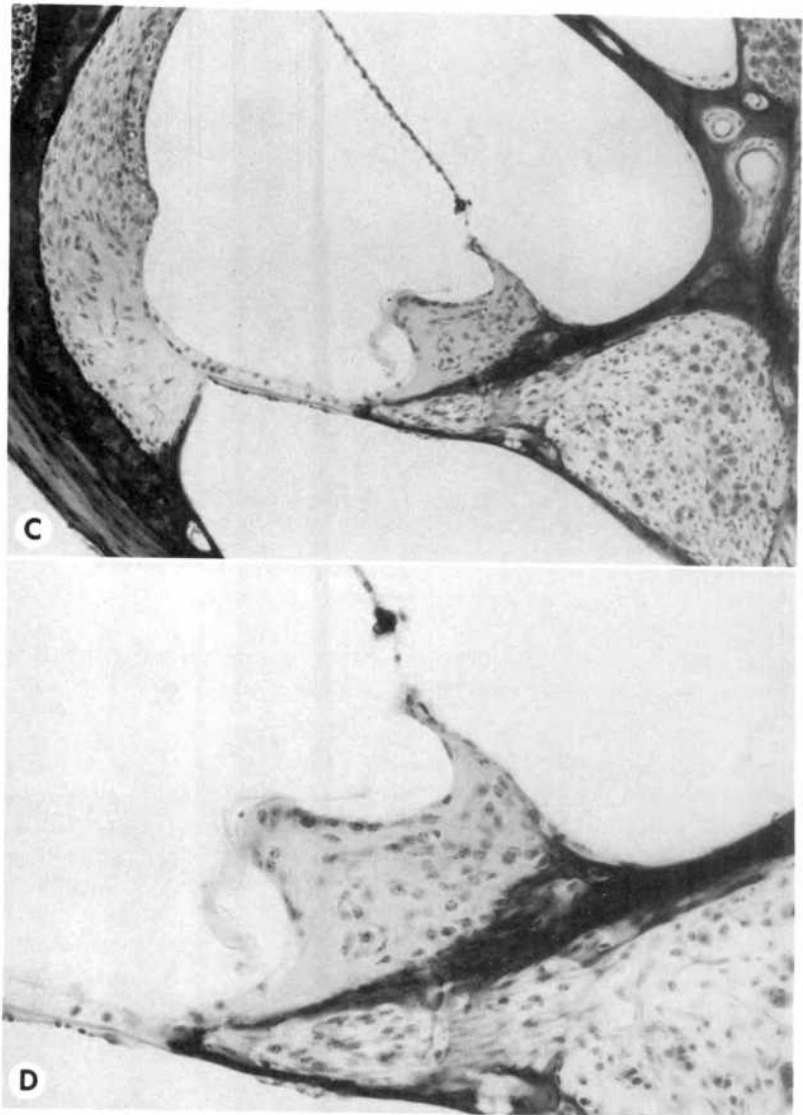
of Corti was observed throughout all turns of all mutant cochleas. Severity of degeneration varied, with some turns showing total loss of hair cells, supporting cells, and pillar cells, while other turns still showed pillar cells or supporting cells and an occasional isolated inner hair cell (Fig 3). No instance of intact outer hair cells was observed. Involvement of the hook portion of the cochlea could not be adequately assessed because of the plane and thickness of the sections. The pattern of degeneration of the organ of Corti was bilaterally symmetric in all five MOS-3 animals, with little if any intrasubject variability. However, there was intersubject variation. Two of the five MOS-3 animals showed organ of Corti degeneration progressively worse from base to apex, two showed degeneration progressively less from base to apex, and one showed uniform degeneration throughout all turns. In contrast to the variability of the gradient of degeneration apparent in the organ of Corti, a gradient of degeneration of spiral ganglion cells progressively less from base to apex was observed in all five animals (Fig 3).

Vestibular end organs showed more subtle abnormalities than the cochlea. The cristae ampullares of all semicircular canals appeared normal, as did the endolymphatic duct and sac. Cell bodies of Scarpa's ganglion and their peripheral processes appeared normal in size and density. Utricular and saccular hair cells were unremarkable. Otoconia of the mutant utricles and saccules were abnormal in all cases. The mutant otoconia were larger than normal and far fewer in number (Fig 4).

DISCUSSION

In normal mouse tissues the *mos* proto-oncogene is tightly regulated. Low levels of *mos* mRNA are expressed in adult brain, kidney, mammary gland, and epididymis, as well as in 18- to 19-day embryos.³ It has recently been shown that the *mos* protein is essential for oocyte meiotic maturation,^{4,5} and that it is a candidate initiator of maturation-promoting factor.⁶ In the FVB/N transgenic strain used in the current study, in situ hybridization has been used to demonstrate *mos* overexpression in tissues showing

Fig 2, continued. C) Low-power view of MOS-3 specimen (original x100). Note total loss of hair cells, supporting cells, and pillar cells. Tectorial membrane appears grossly normal but somewhat contracted. Normally convex surface of spiral limbus is scooped out in deep trough. There is marked loss of spiral ganglion cells in Rosenthal's canal. D) High-power view of same MOS-3 specimen (original x200). Note normal-appearing stellate stromal cells in middle portion of spiral limbus but loss of interdental cell palisade.



pathologic changes, and an S1 nuclease protection assay detected RNA expression of the transgene in all tissues examined, with particularly high levels in brain.¹ Propst et al¹ have suggested that inappropriate expression in somatic cells of a protein involved in shifting resting oocytes into meiosis could interfere with the induction or maintenance of the differentiated state. They have alternatively proposed that overexpression of the protein serine-threonine kinase *mos* might disturb the intricate balance of protein phosphorylation that regulates cellular differentiation and function, particularly in the brain, thus explaining the need for tight regulation of *mos* expression during development and in differentiated cells.

It is tempting to conclude that the pathologic findings in MOS-3 all represent overexpression of *mos* gene product due to deregulation. Another hypothesis is that they are a result of alteration of function of a normally occurring gene adjacent to the insertion site of the *mos* transgene. Since only one strain of transgenic animals was used in the

present study, this question cannot be resolved. Comparison of findings in the other strains (some of which have only a single copy of *mos* per haploid genome, compared to three or four copies in MOS-3) would clarify this issue. Furthermore, since all animals used in this study were the same age, it cannot be determined which of the findings are developmental, resulting from deregulation or overexpression of the gene during critical phases of embryogenesis, and which may be degenerative, due to the result of primary action of *mos* gene product on target tissues or secondary effects of dysfunctional target tissues during maturation after birth.

Behavioral measures of hearing threshold in the mouse have demonstrated a cochlear frequency spectrum from 0.5 to 100 kHz.⁷ In the present study BAEPs were selected as a screening test of auditory system function. The broadband click stimulus used was delivered through a speaker with 1 to 20 kHz nominal bandwidth. Therefore, only a portion of the cochlea was actually tested. Although morphologic findings are consistent with a probable

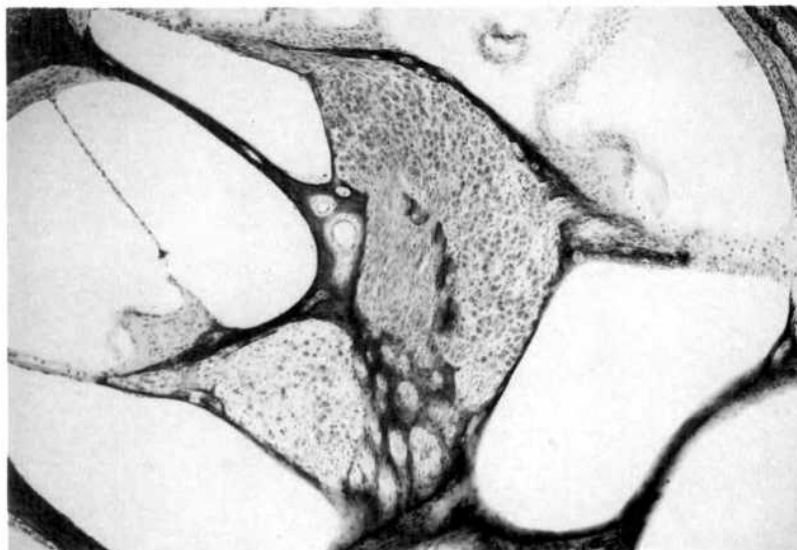


Fig 3. Low-power view of 20- μ m midmodiolar section of MOS-3 cochlea (H & E, original x40). Note total loss of organ of Corti in most basal turn (same as in Fig 2) but pillar cells still identifiable in degenerating organ of Corti in next most apical turn. There is obvious gradient of spiral ganglion cell loss that is worst at basal end of cochlea and gets progressively less severe toward apex.

hearing loss across the entire frequency spectrum, threshold testing using tonal stimuli would be necessary to confirm this or identify any frequency domain with hearing preservation.

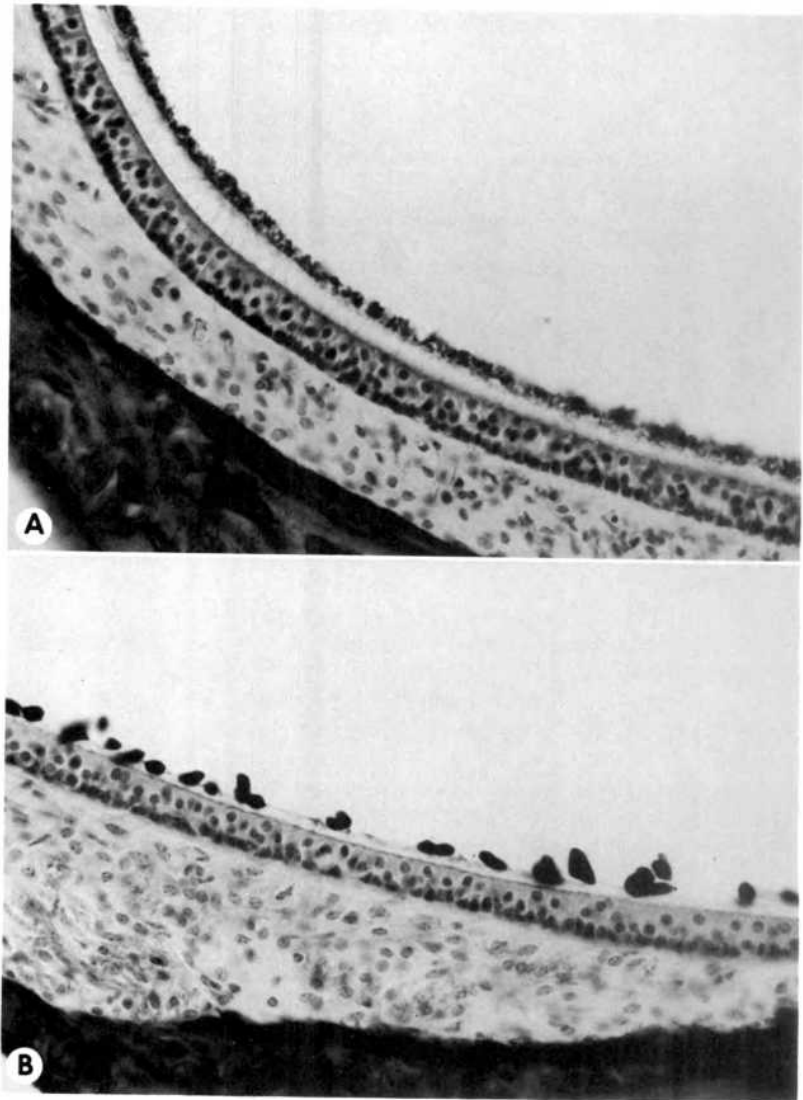
No prior reports of gross pathologic changes of the shape of the spiral limbus exist. Kimura et al⁸ have reviewed normal and pathologic morphology of the spiral limbus and note that the supporting cells and regions adjacent to the inner sulcus are highly susceptible to toxic, inflammatory, traumatic, and vaso-occlusive injury. Such lesions, even when severe, spare the interdental cells. If the organ of Corti is also affected, outer hair cells are absent. The common factor associated with all instances of spiral limbus cell atrophy in their study was alteration of ground substance due to contamination of perilymph. They conclude that alteration in the spiral limbus may serve as one of the most sensitive indicators of altered perilymph composition. None of the pathologic findings described include alteration of the overall convex shape of the spiral limbus, however. The functional significance of the trough-shaped deformity of the spiral limbus observed in MOS-3 is unclear. The palisade of interdental cells secretes glycoproteins believed essential in the development of the tectorial membrane.⁹⁻¹¹ The observation of apparently normal tectorial membrane in MOS-3 despite grossly abnormal spiral limbus raises questions about this role of the interdental cells. Another possible explanation for the finding of a normal tectorial membrane and abnormal spiral limbus is that the interdental cells are present and functionally normal but the supporting stromal cells are abnormal, resulting in a deformity of the convex surface. A small capillary is often present at the junction of the spiral limbus and Reissner's membrane (K. Steele, personal communication, 1990). The trough-shaped deformity of the spiral limbus could represent a massive dilatation of this vascular channel. If, as some have suggested, the spiral limbus plays a role in fluid, ion, or

protein transport,^{10,12-15} the gross distortion of the spiral limbus in MOS-3 raises the possibility of impairment of any or all of these transport functions. This could, in turn, contribute to degeneration of the organ of Corti.

Propst et al¹ have reported that the primary pathologic defect in neurons in *mos* transgenic animals appears to be swelling of the neuronal processes followed by degeneration of the axon. The finding of a gradient of spiral ganglion cell degeneration worst in the base of the cochlea and progressively less toward the apex in conjunction with varying patterns of organ of Corti degeneration (base to apex, apex to base, or uniform) suggests that degeneration of the spiral ganglion and organ of Corti may not be directly related as in retrograde neuronal degeneration following hair cell loss. In other words, it is possible that the spiral ganglion degeneration represents the primary neuropathologic lesion of *mos* overexpression as noted throughout the central nervous system, while the hair cell degeneration may be due to direct action of *mos* gene product on hair cells, may be secondary to spiral limbus dysfunction, or may be due to a combination of these factors and others. Organ of Corti degeneration in MOS-3 mice is similar in both cochleas of each individual in all cases, but there is variation among individuals. This observation does not help us differentiate between the possibility of a primary *mos* gene action on differentiation or maintenance of hair cells and the possibility of a diffuse toxic effect of abnormal ionic milieu.

Otoconial abnormalities noted in MOS-3 are similar to those noted in other animals. Genetic anomalies of otoconia have been reported for several species.¹⁶⁻¹⁹ These anomalies have included absence of otoliths, as well as altered elemental content or dysmorphology. Otoconial anomalies have been induced by dietary changes, prenatal irradiation, and ototoxic drugs.²⁰⁻²⁵ The secretion of both the organ-

Fig 4. High-power 20- μ m sections of saccular macula (H & E, original $\times 200$). A) Control animal. B) MOS-3 animal. Note large, clumped, dysmorphic otoconia.



ic (glycoprotein) and inorganic (calcium carbonate as calcite) components of otoconia is precisely regulated and occurs during a specific time interval in embryogenesis.²⁶⁻²⁸ Maintenance of otoconial structure is dependent, at least in part, upon endolymph composition.²⁹ The anomalies of increased size and decreased number of saccular and utricular otoconia observed in MOS-3 mice may represent abnormal otolith development, faulty otolith maintenance, or a combination of the two. Otoconial abnormalities in experimental animals are associated with behavioral vestibular symptoms if more than 70% to 80% of the otoconia are missing.³⁰ It is not clear whether the head tilt and circling behavior of MOS-3 animals is due solely to the otoconial anomaly or whether involvement of the central vestibular pathways is also a factor.

SUMMARY

Brain stem auditory evoked potentials were measured and temporal bone histopathology surveyed in representatives of one of several lines of trans-

genic mice carrying the *c-mos* proto-oncogene. The *mos* gene product is believed essential for maturation and maintenance of differentiation of specific cell types, but is normally found only in low levels in specific tissues and during specific periods during embryogenesis. These transgenic animals reportedly demonstrate elevated levels of *mos* mRNA in all adult tissues. The MOS-3 line, carrying three to four copies of the transgene per haploid genome, was used for the current study. The MOS-3 animals had no detectable hearing by evoked response audiometry. Temporal bone histopathologic changes of transgenic mice include structural deformity of the spiral limbus, degeneration of the organ of Corti, degeneration of the spiral ganglion, and abnormal otoconia. These histopathologic findings may be degeneration due to primary action of *mos* gene product upon target tissues, may be secondary effects due to dysfunctional target tissues, or may be congenital, resulting from deregulation and overexpression of *mos* gene product during critical phases of embryogenesis.

ACKNOWLEDGMENT — The author acknowledges the advice, technical assistance, and acquisition of animals by Paul E. Neumann, MD.

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INNER EAR DAMAGE AND PASSAGE THROUGH THE ROUND WINDOW MEMBRANE OF *PSEUDOMONAS AERUGINOSA* EXOTOXIN A IN A CHINCHILLA MODEL

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By the use of computer-assisted morphometric analysis of the organ of Corti and/or measurements of action potential threshold changes, inner ear changes in chinchillas were evaluated 4 weeks after application on the round window membrane of a *Pseudomonas aeruginosa* exotoxin A solution. Severe inner ear damage was detected after application of 50 ng (5 μ L at a concentration of 10 μ g/mL) exotoxin A, whereas application of 5 ng exotoxin did not cause measurable inner ear damage. Perilymph concentrations of exotoxin A were measured with an enzyme-linked immunosorbent assay 1.5 to 19 hours after 50 ng, 0.5 μ g, or 5 μ g of exotoxin A was applied on the round window membrane. Only the highest concentration produced measurable levels of exotoxin in the inner ear fluids. It is concluded that exotoxin A present on the round window membrane of the chinchilla has the ability to penetrate into the inner ear and cause irreversible inner ear changes.

KEY WORDS — *Pseudomonas aeruginosa* exotoxin A, round window membrane permeability, sensorineural hearing loss.

INTRODUCTION

Prolonged chronic suppurative otitis media (CSOM) may eventually, without evidence of direct spread of the infection into the labyrinth, lead to sensorineural hearing loss (SNHL).¹⁻⁷ The bone conduction threshold change is usually of a mild degree.⁷ Several theories have been put forward in an attempt to explain this phenomenon. Some investigators claim that the bone conduction threshold change seen in this condition reflects a conductive hearing loss mimicking a Carhart's notch as seen in otosclerosis.^{3,6,7} Others support the theory that the SNHL reflects true inner ear damage related to passage of ototoxic substances from the middle ear cleft into the inner ear.⁴ Also, treatment has been blamed, since several antibiotics and antiseptics used for local treatment of CSOM have been reported to cause inner ear damage.⁸ Experimentally, the round window membrane (RWM) has been found to be permeable to various substances.⁸⁻¹⁴

Many bacteria found in CSOM have the ability to produce toxins. Endotoxin elicited by gram-negative bacteria has been demonstrated to cause high-frequency hearing loss and cochlear damage when locally instilled in the middle ear of animals at concentrations ranging from 10 μ g/mL to 1 mg/mL.^{14,15} Furthermore, endotoxin has been found in the inner ear after application to the middle ear.¹⁴ Another bacterial toxin, staphylococcal exotoxin, applied to the RWM in doses comparable to what is found in

serum of patients with septicemia, has been shown to be transported into the inner ear.¹¹

Pseudomonas aeruginosa (PA) is frequently cultured from patients with CSOM.¹⁶ It has the ability to produce several cytotoxic products that are considered to be partly responsible for the noxious effects. One of the most interesting substances is PA exotoxin A (PaExoA), which is a highly cytotoxic enzyme with a molecular weight of approximately 70,000 d. Ninety percent of clinical isolates of PA have been shown to produce this toxin, which is regarded as an important factor in the pathogenicity of PA infections.¹⁷ It is highly toxic and the mean lethal dose in mice is as low as 0.06 μ g. After internalization into the cells, the toxin inhibits protein synthesis by inactivating elongation factor 2.¹⁷ Animals injected with lethal doses of PaExoA show hepatocellular necrosis, hemorrhagic lungs, tubular necrosis, and hemorrhage in the kidneys.¹⁷ One can assume that PaExoA can be produced locally in the middle ear that is infected with PA, although no clinical data supporting this assumption have been reported.¹⁸

The aims of this study were to investigate the ototoxic potential and the degree of penetration into the inner ear of PaExoA when applied to the RWM of the chinchilla.

MATERIALS AND METHODS

Exotoxin A. Lyophilized, purified PaExoA (pro-

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duction strain PA-103, Swiss Serum and Vaccine Institute, Bern, Switzerland) was dissolved to a concentration of 1 or 5 mg/mL in 10 mmol/L Tris HCl buffer, pH 8.0, with 5% wt/vol lactose and frozen immediately to -70°C in 20- μL vials. For each experiment and assay, a fresh vial was thawed and used immediately. The concentrated PaExoA was diluted to the appropriate concentration in 0.1 mol/L phosphate-buffered saline (PBS) at pH 7.4. The same batch of PaExoA was used throughout the entire study.

Operative Procedure. Previously healthy chinchillas (*Chinchilla laniger*) with a body weight of 400 to 600 g were used. Prior to each experiment, both tympanic membranes were examined and found to be normal with an operating microscope, and normal tympanograms were obtained with a conventional tympanometer (Grason-Stadler). The animals were anesthetized with ketamine HCl injected intramuscularly in a dose of 40 mg/kg. The operating procedure was performed under sterile conditions and took approximately 20 minutes for each animal. The middle ear was opened posteriorly to expose the RWM. From this point, a surgical microscope was used. In order to get access to the RWM, a thin septum of bone posterior to the RWM was removed. Sterile Gelfoam powder (0009-0433-01, Upjohn Co), soaked in 5 μL (± 2) PaExoA solution, or PBS only (control ears), was applied to the RWM. The transected muscles and the skin were then sutured back in place.

Toxicity Study. A total of 27 animals were used. The right RWMs of 2 animals were exposed to PaExoA concentrations of 50 $\mu\text{g/mL}$ (group A), those of 18 animals to 10 $\mu\text{g/mL}$ (group B), and those of 7 animals to 1 $\mu\text{g/mL}$ (group C). The left ears, which served as controls, were exposed to PBS only.

In order to detect infections postoperatively, the following procedure was performed. Tympanograms were obtained and the tympanic membranes on both sides were observed in the operating microscope without anesthesia after 2 days, 4 days, and 1, 2, 3, and 4 weeks. These examinations were done in the majority of animals at 2 and 4 days and in all animals at later time intervals.

The tympanograms were classified as follows. Type A had a tympanogram peak between -100 and $+100$ decapascals. Type C1 had a peak between -100 and -200 decapascals. Type C2 had a peak less than -200 decapascals. Type B was a flat curve without a distinctive peak. Type E (for error) was one in which, in spite of repeated attempts, no recording was achieved.

The microscopic appearance of the tympanic membrane was classified as follows. Type N (for normal) was one in which no evidence was found of a disorder of the tympanic membrane or the middle

ear. Type RM (for red mucosa) was a normal tympanic membrane with hyperemia of the middle ear mucosa. Type F (for fluid) showed evidence of translucent middle ear fluid. Type P (for purulent) had purulent drainage from the middle ear or a bulging hyperemic tympanic membrane.

The ears were considered to be free from postoperative infection if the middle ear fluid that developed was nonpurulent and if the tympanograms improved over time. Because of the risk of introducing infection or inducing hemorrhage in the middle ear, none of the middle ears that were determined to be free from postoperative infection were cultured during the course of the experiment. Animals that were classified as type P were taken out of the study.

The 2 animals in group A were studied with computer-assisted morphometric analysis (CAMA).^{19,20} In group B, 6 animals had to be painlessly killed because of ear infections in 3 (type B tympanogram curves), wound infection in 1, and prolapse of the intestine in 1 before the end of the experimental period. One animal died for unknown reasons. Of the remaining 12 animals, 4 were studied with CAMA only, 5 with measurement of action potential threshold (APT) only, and 3 with both CAMA and APT. In group C 1 animal developed a wound infection and 1 a severe infection of the forehead and they were consequently taken out of the study. The remaining 5 animals were studied with both CAMA and APT.

Four weeks after exposure to PaExoA, complete hard surface preparations of the organ of Corti were studied with CAMA. The cochleas were prepared according to a method described by Santi et al.^{19,20} The organ of Corti was studied at 1,000 times magnification in a phase-contrast microscope. The presence or absence of outer and inner hair cells was recorded. A missing hair cell was defined as a completely absent hair cell with no detectable cell body or nucleus. When the supporting cells were preserved, an absent hair cell was recorded when a phalangeal scar had replaced the hair cell. The computerized mapping and measurement of each cochlea made it possible to record all absent hair cells in the cochlea. From these data, relative hair cell loss in each of 10 equal segments of the total length of the cochlea was calculated. Normative data of hair cell density in each of 10 equal segments of the chinchilla cochlea were obtained from a previous publication.²¹ An average outer hair cell loss of 96 (range, 14 to 506) and inner hair cell loss of 12 (range, 0 to 111) in 51 approximately 1-year-old normal chinchillas have previously been found in our own laboratory.²⁰

The APT was measured as previously described by Morizono and Sikora.²² The same method of anesthesia was used as above. No attempt was made to

TABLE 1. PATHOLOGIC FINDINGS AFTER APPLICATION OF *PSEUDOMONAS AERUGINOSA* EXOTOXIN A OR PHOSPHATE-BUFFERED SALINE

Animal No.	Middle Ear Findings After 1 Week		Inner Ear Damage After 4 Weeks	
	Left (Cont)	Right (PaExoA)	Left (Cont)	Right (PaExoA)
A1	A, N	A, N	—	+
A2	A, N	A, N	—	+
B1	C1, F	C1, F	—	+
B2	C1, N	A, N	—	+
B3	A, N	A, N	—	—
B4	A, N	C1, N	—	+
B5	A, N	C1, F	—	+
B6	A, N	A, N	—	—
B7	A, N	C1, F	—	—
B8	C1, N	B, F	—	+
B9	C1, F	A, N	—	+
B10	A, F	C1, RM	—	+
B11	C1, F	A, F	—	+
B12	C1, F	C1, F	—	+
C1	C1, RM	A, N	—	—
C2	A, N	C1, F	—	—
C3	C1, RM	A, RM	—	—
C4	E, N	E, F	—	—
C5	A, N	A, RM	—	—

Agents were applied to round window membrane via soaked Gelfoam.

Cont — control (ie, phosphate-buffered saline), PaExoA — *Pseudomonas aeruginosa* exotoxin A, A — tympanogram with peak between -100 and +100 decapascals, N — normal findings on microscopy, C1 — tympanogram with peak between -100 and -200 decapascals, F — serous fluid in middle ear, B — flat tympanogram curve without distinctive peak, RM — red mucosa in middle ear without evidence of fluid, E — recording error.

remove the remaining Gelfoam, since that might have caused rupture of the RWM.

Permeability Study. A total of 26 animals were used. The operative procedure was the same as in the toxicity study. The animals were divided into three groups. In group I ($n = 5$), the normal RWM on the right side was exposed to PaExoA at a concentration of 10 $\mu\text{g/mL}$. In group II ($n = 9$), the normal right RWM was exposed to 0.1 mg/mL. In group III ($n = 12$), 7 animals were exposed to 1.0 mg/mL on the right side only. Since no PaExoA was detected on the nonexposed side of these animals, the remaining 5 animals were exposed to PaExoA at a concentration of 1.0 mg/mL on both RWMs. The ears in the three groups not subjected to PaExoA were not operated on before the sampling of perilymph.

In group I, two animals were sampled after 6 hours and the remaining three after 18 hours. In group II, three animals were sampled after 3 hours, three after 6 hours, and three after 24 hours. In group III, four animals were sampled after 1 hour 30 minutes, five after 3 hours, and three after 19 hours. Anesthetic was given as described above. The Gelfoam was removed from the RWM and the entire middle ear cavity was irrigated slowly with approximately 100 mL of 0.9% NaCl. Before emptying the middle ear, irrigating fluid was sampled as a control for analysis of PaExoA content. The

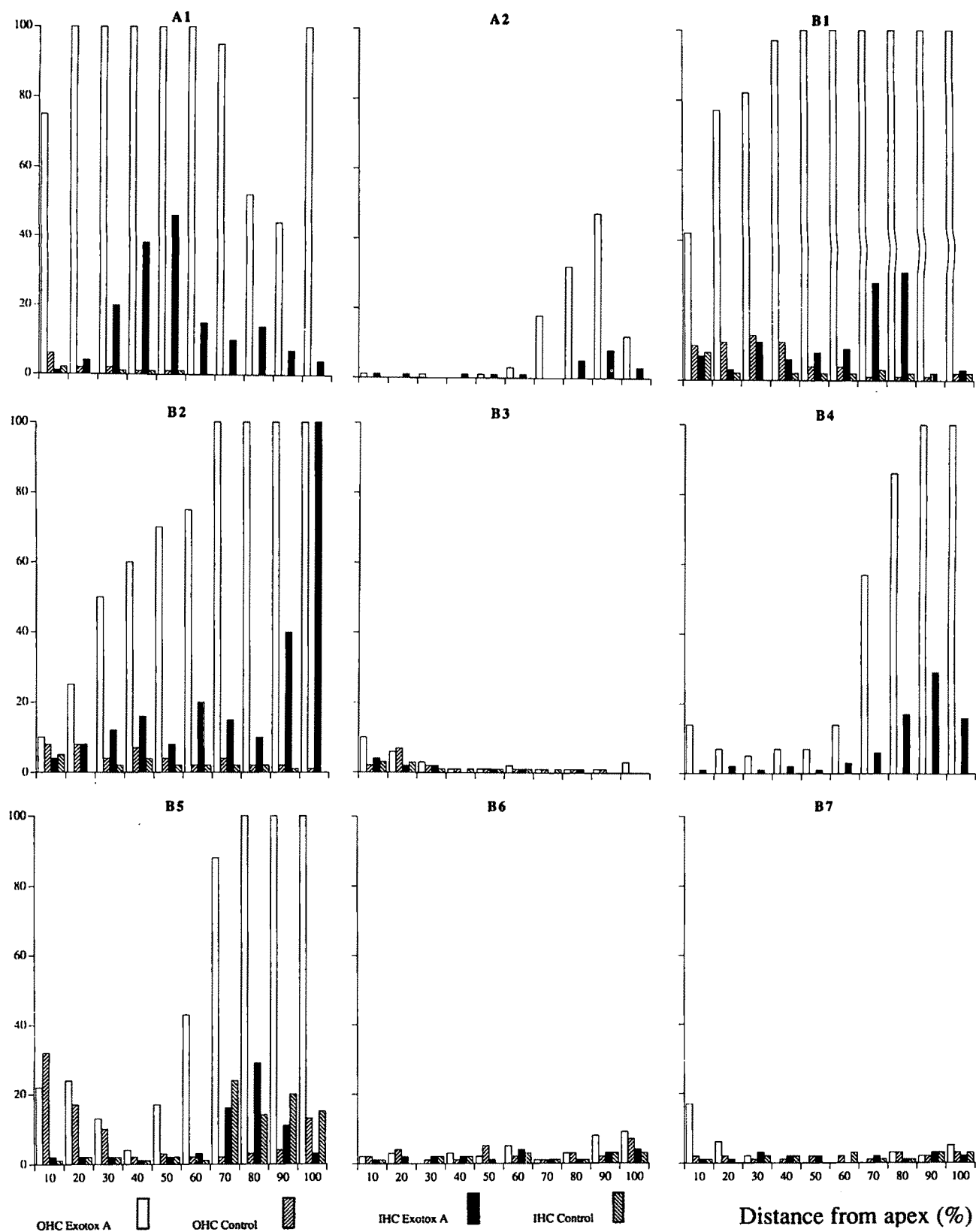
middle ear, the RWM area in particular, was carefully dried with blotting paper. After the stapes had been pushed into the vestibulum a thin glass capillary was inserted through the RWM and perilymph was removed with slight suction. Sampling time was approximately 10 seconds. The volume obtained ranged from 5 to 16 μL . In the nonexposed ears, perilymph was sampled in the same way without previous irrigation of the middle ear cavity.

All samples were analyzed within 6 hours with enzyme-linked immunosorbent assay (ELISA) according to Øgaard et al.²³ Sheep anti-PaExoA and rabbit anti-PaExoA were obtained from the Swiss Serum and Vaccine Institute. The perilymph samples were diluted according to the following scheme. Each sample in groups I and II was diluted with 0.45 mL PBS-Tween and further diluted 5, 25, and 125 times. In order to improve the detection limit in group III, the samples were diluted with 0.15 mL PBS-Tween and further diluted 5, 25, and 125 times. Each dilution of the samples from groups I and II was analyzed in duplicate. Because of the low volume of the first dilution in group III, it was not possible to analyze the first dilution of the samples more than once. The subsequent 5-, 25-, and 125-times dilutions in group III were, however, analyzed twice. Two parallel serial dilutions of known concentrations of PaExoA were also set on each plate, serving as standard. The PaExoA concentration in each sample was determined by comparison with the standard curve between 0.5 and 6 ng/mL.

RESULTS

Toxicity Study. Within the first week nine animals were taken out of the study because of infectious complications mainly affecting the middle ears or the surgical wound. Four PaExoA-exposed ears and three control ears were affected. A summary of the microscopic findings of the tympanic membrane and the tympanograms after 1 week in the remaining animals is presented in Table 1. Thirty-three ears out of 38 developed middle ear damage during the experiment, discovered either as a pathologic tympanogram or as a pathologic microscopic finding. Maximum pathologic change was found within 1 week after operation, whereafter it declined. Five ears (B2R, B5L, B6L, C2L, and C5L) were considered to be normal during the whole 4-week period. During the 4-week period, the middle ears gradually recovered, with a change toward a normal tympanogram and a normal appearance of the tympanic membrane. All middle ears except 1 (B12L) were after 4 weeks considered to be normal. After decapitation all middle ears except B12L appeared to be normal on gross examination, except for the RWM region, in which Gelfoam still remained in all animals in both ears. Animal B4 developed ataxia with symptoms of left vestibular impairment; however, it had no signs of

Hair cell loss (%)



Individual cytochrome c histograms showing percentage hair cell loss in ears exposed 4 weeks earlier to *Pseudomonas aeruginosa* exotoxin (Exotox A) at concentration of 50 $\mu\text{g/mL}$ (A1 and A2) or 10 $\mu\text{g/mL}$ (B1 through B7). Control ears were exposed to phosphate-buffered saline only. Control ear of animal B4 is not included. OHC — outer hair cells, IHC — inner hair cells.

TABLE 2. SUMMATED ACTION POTENTIAL THRESHOLDS IN DECIBELS IN ANIMALS EXPOSED TO *PSEUDOMONAS AERUGINOSA* EXOTOXIN A ON RIGHT ROUND WINDOW MEMBRANE

No.	2 kHz		3 kHz		4 kHz		6 kHz		8 kHz		12 kHz		16 kHz	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R
B5	38.0	>70.0	47.9	64.8	58.3	>70.0	61.8	>70.0	40.3	>70.0	62.1	>70.0	64.4	>70.0
B6	26.7	28.2	30.5	36.0	17.8	25.5	25.1	25.1	24.1	24.1	23.9	31.2	43.2	41.0
B7	31.5	39.3	34.2	31.6	25.9	25.5	21.8	27.4	11.2	16.3	22.3	38.5	45.5	54.0
B8	41.1	>70.0	41.5	>70.0	47.0	>70.0	46.0	>70.0	34.2	>70.0	37.0	>70.0	62.5	>70.0
B9	29.8	>70.0	39.1	>70.0	50.6	>70.0	48.9	>70.0	55.4	>70.0	41.4	>70.0	63.6	>70.0
B10	46.8	>70.0	49.1	>70.0	44.3	>70.0	42.9	>70.0	39.1	>70.0	37.7	>70.0	50.1	>70.0
B11	43.8	>70.0	52.6	>70.0	48.7	>70.0	39.6	>70.0	37.1	>70.0	44.0	>70.0	51.8	>70.0
B12	36.9	>70.0	33.4	>70.0	28.4	>70.0	40.8	>70.0	34.7	>70.0	47.3	>70.0	60.7	>70.0

Exposure concentration was 10 $\mu\text{g/mL}$.

purulent middle ear infection. The left cochlea from that animal was filled with inflammatory debris that made it impossible to obtain a hard surface preparation of that ear. The middle ear damage described above and in Table 1 was equally distributed between the exposed ears and control ears, and between ears with inner ear damage (7/11 or 63%) and ears without inner ear damage (19/27 or 70%). Middle ear damage was not more frequent in the higher-dose groups (10 and 50 $\mu\text{g/mL}$) as compared to the lower-dose group (1 $\mu\text{g/mL}$). The middle ear damage observed in the ears that developed inner ear damage was not worse than the middle ear damage observed in the ears that did not develop inner ear damage.

Comparative cytochleograms of cochlear hard surface preparations obtained from groups A and B are presented in the Figure. Both animals exposed to PaExoA at a concentration of 50 $\mu\text{g/mL}$ (A1 and A2) had substantial hair cell loss on the exposed side as compared with the unexposed side. Animal A1 had 91% loss of outer hair cells and 24% loss of inner hair cells, with the maximum damage located in the middle region of the organ of Corti. Animal A2 had more discrete changes, with 15% to 50% loss of outer hair cells in the base, in contrast to the contralateral ear, with approximately 10 missing hair cells in the entire cochlea. Four of the animals in group B (B1, B2, B4, and B5), exposed to PaExoA at a concentration of 10 $\mu\text{g/mL}$, had major hair cell loss, mostly affecting the basal coil. Three animals (B3, B6, and B7) had minimal hair cell loss within the normal range²⁰ and a symmetric distribution between both cochleas. The somewhat increased loss of hair cells found in the control ear of animal B5 is within the range of hair cell loss found in healthy animals.²⁰ There is, however, a great difference in hair cell loss between the exposed and control ears of this animal, with an almost total outer hair cell loss in the base of the exposed ear. The APT data from this control ear also reveal a greater threshold change than those from the other control ears.

All three outer hair cell rows were damaged. There was a tendency toward more excessive damage in rows 2 and 3 as compared with row 1, with the exception of animal B1, in which row 1 was more damaged than rows 2 and 3, and animals A1

and A2, which had equal damage of all outer hair cell rows. In addition to the quantitative findings, many of the remaining hair cells adjacent to the damaged areas showed various degrees of stereociliary damage. Generally, the severity of the morphologic changes, as well as the hair cell loss, gradually increased from the inner hair cell row toward the third row of outer hair cells. The control ears were comparable to ears of normal animals²⁰ with respect to hair cell loss and morphologic appearance.

The APT measurements from the ears in group B are presented in Table 2. Three animals (B5, B6, and B7) in group B were examined with both CAME and APT measurements. In animal B5 no APT could be obtained on the exposed side and the animal was consequently considered to be deaf on that side. The control side of animal B5 had APTs in most frequencies approximately 20 dB above the mean thresholds for the control ears. The findings on CAME were within the normal range in this ear. No difference in APT between the exposed ear and the control ear was found in animals B6 and B7. The APT findings in these animals corresponded well with the result of the CAME. The APT measurements only were performed in animals B8 through B12. No APT could be obtained at any frequency in any of these animals on the PaExoA-exposed side, in contrast with the control ears of the same animals. These animals were consequently considered to be deaf on the exposed side.

In group C, exposed to PaExoA at a concentration of 1 $\mu\text{g/mL}$ and examined with CAME, there was no difference between the exposed ear and the control ear. In four of these animals a mild hair cell loss was noted to be bilateral and symmetric throughout the cochlea and was considered to be within the range of the scattered hair cell loss seen in normal unexposed animals.²⁰ One animal had symmetric losses of 261 and 234 outer hair cells in each cochlea, respectively, and this loss was mainly located in the apical part of the cochlea. In comparing the APT of the exposed ear with those of the unexposed ears in group C, no difference could be detected between the two ears.

Permeability Study. The ELISA assay proved to be highly reproducible and the detection limit for

TABLE 3. *PSEUDOMONAS AERUGINOSA* EXOTOXIN A CONCENTRATION IN PERILYMPH AFTER EXPOSURE OF ROUND WINDOW MEMBRANE

Animal No.	Exposure Time (h)	Left Ear (ng/mL)	Right Ear (ng/mL)
Unilateral exposure to right ear			
III1	1.5	<7	<6
III2	1.5	<6	<6
III3	1.5	<6	18
III4	1.5	<6	9
III5	3.0	<6	NP
III6	3.0	<6	5,600
III7	3.0	<6	209
Bilateral exposure			
III8	3	467	618
III9	3	1,706	132
III10	19	275	<41
III11	19	<28	33
III12	19	27	29

Exposure concentration was 1 mg/mL.

NP — no perilymph obtained owing to technical problems.

PaExoA was 0.5 ng/mL. The background activity during all experiments was low and constant.

None of the animals whose middle ears had been exposed to PaExoA at a concentration of 0.1 mg/mL or less (groups I and II) demonstrated any detectable PaExoA in perilymph at the time of sampling. The detection limit for these two groups ranged between 12 and 33 ng/mL.

The samples in group III were not diluted to the same degree as the samples in groups I and II, and thus had a lower detection limit (6 ng/mL). Data from group III are presented in Table 3. Two of the animals exposed for 1.5 hours (III1 and III2) did not have detectable levels of PaExoA in perilymph on the PaExoA-exposed side, while the concentrations on the exposed sides of the other two animals (III3 and III4) were 9 and 18 ng/mL, respectively.

Five animals in group III were exposed to PaExoA for 3 hours. Out of these, three were only unilaterally exposed (III5, III6, and III7), while the remaining two were bilaterally exposed (III8 and III9). The exotoxin level in perilymph in this group ranged from 132 to 5,600 ng/mL. Owing to technical problems, no perilymph could be obtained from the exposed ear in one of the animals (III5), but perilymph in the unexposed ear of this animal was free from PaExoA.

All three animals in group III that were exposed to exotoxin for 19 hours were bilaterally subjected to PaExoA. In two of these ears (III10 R and III11 L) PaExoA could not be detected in perilymph. In the remaining four ears (III10 L, III11 R, III12 L, and III12 R) the concentrations of PaExoA in the perilymph were 275, 33, 27, and 29 ng/mL, respectively. No PaExoA could be detected in any of the control ears.

The rinsing fluid, which was analyzed after the removal of exotoxin and prior to the sampling of

perilymph, was negative (<0.5 ng/mL) for presence of PaExoA in all animals belonging to groups I and II. In group III the rinsing fluid was mostly negative (<0.5 ng/mL), except for low values between 1 and 3 ng/mL in animals III5 L, III8 L, III9 L, III9 R, and III12 L.

DISCUSSION

Little is known about the mechanism underlying the development of inner ear damage in the course of CSOM. The production of potentially ototoxic bacterial products in the middle ear may contribute to the inner ear changes. This has been demonstrated experimentally for endotoxins in high concentrations.^{14,15} Several investigators have shown that the RWM is permeable to macromolecules (albumin and horseradish peroxidase) of the same size as PaExoA.^{9,11,13} It is therefore enticing to postulate that PaExoA has the ability to cross the RWM and cause cochlear damage. Only few data can be obtained regarding tissue concentration of PaExoA. Most PA strains cultured from the middle ear can be considered to be potential toxin producers.^{17,18} Production of PaExoA has been demonstrated in patients with cystic fibrosis infected with PA, in burned skin of animals infected with PA, and in animal lung tissue chronically infected with PA.^{17,24-26} In infected, burned skin the tissue concentration of PaExoA has been estimated to be 2 ng/ μ g protein,²³ and in culture supernatants, up to 1 μ g/mL.²³ The exotoxin contributes to the destruction of biologic barriers seen in PA infections, and because of the frequent occurrence of PaExoA in PA infections in general, it may be assumed that PaExoA may also be released into the middle ear. Few facts, however, are established about the occurrence and importance of PaExoA in chronic ear infections.

The majority of the animals eliminated from the study developed infections in the middle ear that could have affected their inner ears. With a peak incidence within 1 week after operation, the majority of the animals included in the study developed mild middle ear damage (Table 1). This could have been caused by a mild, self-healing infection introduced at the time of operation or by operative trauma. It is, however, unlikely that the inner ear changes could be attributed to a subclinical middle ear infection, since there was no preponderance of development of middle ear damage in the PaExoA-exposed ears. The different dosage groups were also equally affected. In addition, PaExoA placed in the RWM niche did not produce more severe middle ear inflammation than did instillation of PBS, as determined by impedance measurements and inspection of the tympanic membrane.

The APTs obtained from the control ears varied considerably and were generally higher than one might expect from a normal ear. The thresholds were, however, comparable to what has been found

in animals directly after placing Gelfoam on the RWM (data not presented).

The cytochleograms demonstrate that the damage to the organ of Corti produced by PaExoA at concentrations at or above 10 $\mu\text{g/mL}$ varied considerably. This variability may be due to technical difficulties in exposing each RWM to exactly the same amount of PaExoA, to differences in sensitivity of the organ of Corti, or to individual differences in RWM permeability. In most of the animals with major damage of the inner ear, the pathologic changes seemed to be most pronounced in the basal part of the cochlea. This finding is in accordance with the distribution of cochlear damage found in other ototoxicity studies.¹⁵ In exposing the RWM to one 10th of this dose (1 $\mu\text{g/mL}$) of PaExoA, neither hearing impairment nor hair cell loss could be demonstrated. In this particular experimental setup, a threshold for the ototoxicity potential of PaExoA applied as a single dose to the RWM was established to be somewhere between 1 and 10 $\mu\text{g/mL}$.

The ELISA used for detection of PaExoA proved to be reproducible, with a high sensitivity and specificity comparable to those of previous experiments performed by other investigators.²³

It was demonstrated that irreversible cochlear damage was induced by an application of 50 ng (5 μL at a concentration of 10 $\mu\text{g/mL}$) of PaExoA on the normal RWM. When the same concentration of PaExoA was applied to the RWM, it was not possible to detect any exotoxin in the perilymph (detection limit between 12 and 33 ng/mL) during a 24-hour period. In spite of a highly sensitive detection method, the amount of PaExoA applied to the RWM had to be increased to 5 μg in order for us to detect the toxin in the inner ear. On this basis we conclude that it is highly improbable that detectable PaExoA levels could occur at any time in perilymph after exposure of the RWM to exotoxin at a concentration of 10 $\mu\text{g/mL}$. The inability of the ELISA to detect PaExoA in the perilymph in the lower dosage groups could be explained partly by inactivation of the toxin in the inner ear or by transport of the toxin from the inner ear fluids to the intracellular compartment. There is also a potential risk for dilution of the perilymph samples due to contamination with cerebrospinal fluid via the cochlear aqueduct and endolymph via rupture of Reissner's membrane. The detection limit for the samples in groups II and III was also somewhat higher (12 to 33 ng/mL versus 6 ng/mL). In view of the concentration gradient over the RWM estimated from the perilymph concentrations in group I (1 mg/mL), however, it seems unlikely that PaExoA may be detected in perilymph after exposure of the RWM to a concentration 100 times lower (10 $\mu\text{g/mL}$).

The passage of PaExoA into the inner ear initially appeared to take place 90 minutes after application.

Higher perilymph levels were found after 3 hours, but still the concentration on the inner ear side was only about 1/1,000 of the estimated concentration on the middle ear side. A rapid decrease in concentration of PaExoA in Gelfoam placed in the middle ear has been found. After 3 hours the concentration decreased to approximately 20%, and after 18 hours to approximately 1% of the original concentration (data not presented). The reason for the rather high perilymph concentrations measured in two ears (III6 R and III9 L) is unclear, but it might be an individual variation in permeability between each RWM, or an artifactual leakage through the RWM.

Detection of PaExoA is not likely to be due to contamination with PaExoA remaining in the middle ear, since only traces of toxin were found in the last portion of the rinsing fluid.

Three animals (III5, III6, and III7) exposed unilaterally to PaExoA at a concentration of 1 mg/mL for 3 hours did not have any measurable levels of PaExoA on the contralateral side. Presumably, therefore, PaExoA is not transported to the contralateral side in detectable amounts. This is in contrast with the findings of Goycoolea et al.¹¹ This discrepancy could be due to the difference in mobility between the highly mobile exotoxin from *Staphylococcus aureus* and PaExoA, or to the small amount of PaExoA applied to each animal.

It was demonstrated that PaExoA placed on the RWM can pass through the RWM in minute amounts. Because of the small number of animals and the possibility of interanimal variations, a clear correlation between the amount of PaExoA placed on the RWM and the level of exotoxin in perilymph was somewhat difficult to establish. Maximum concentration is, however, reached before the conclusion of the experiment, ie, 19 hours of exposure. Compared to the study on endotoxin permeability by Kawauchi et al,¹⁴ who reported a high permeation rate, the present study used a lower total dose of PaExoA. This may, in addition to the rapidly diminishing concentration of PaExoA at the RWM, account for the much higher quotient between middle ear and inner ear concentrations as demonstrated in this study.

The present results indicate that PaExoA can penetrate into the inner ear and cause inner ear damage even in minute amounts. It is shown that the RWM has a low permeation rate for PaExoA. The ototoxic potential is much higher than for endotoxins.¹⁵ The concentration of PaExoA that can be estimated to occur in the infected middle ear cleft is probably much lower than 10 $\mu\text{g/mL}$, which was demonstrated to cause inner ear damage. It is, however, difficult to draw conclusions regarding the pathophysiology of SNHL in CSOM in the human on the basis of animal experiments, since there are many factors that are different in animals. The

normal human RWM is much thicker than the chinchilla one and it also increases in thickness during infectious middle ear disease.¹¹ The human inner ear is therefore probably much more resistant to middle ear infections than the chinchilla inner ear. On the other hand, CSOM is a prolonged disease with an infectious focus present in the middle ear

for months or even years. In order to elucidate the pathophysiology of SNHL in CSOM, it is necessary to investigate all potential sources for this condition. Further studies of middle ear concentrations of bacterial toxins and interactions with local defense systems are needed in order to increase our knowledge concerning this problem.

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THEORETIC ANALYSIS OF MIDDLE EAR GAS COMPOSITION UNDER CONDITIONS OF NONPHYSIOLOGIC VENTILATION

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As gas flows in and out of the nasopharynx, the pressure in that region fluctuates. It drops below or rises above atmospheric pressure, which is itself not constant but is subject to changes in altitude and weather. Such pressure changes in the nasopharynx produce a pumping of gas into and out of the middle ear. The net amount of middle ear gas transferred from or to the nasopharynx will, component for component, in steady state exactly equal the amount of middle ear gas transferred to or from the microcirculation by means of diffusional absorption by (or release from) the mucosa. In the case of a permanently patulous eustachian tube, a single parameter, characteristic of the rate of ventilation through the open eustachian tube, is found to determine the gas composition in the middle ear, whereas in the case of a middle ear ventilated by tympanostomy, two rate-of-ventilation parameters, one for gas flow through the ventilation tube and one for flow through a periodically open eustachian tube, determine the steady state gas composition. A high rate of ventilation favors absorption of oxygen and venting of carbon dioxide from the middle ear in both cases.

KEY WORDS — carbon dioxide, eustachian tube, middle ear, nitrogen, oxygen, pathophysiology, ventilation tube.

INTRODUCTION

The gas contents of the middle ear (ME) are affected 1) by flow of gas into or out of the ME through the eustachian tube (ET), 2) by absorption or release of individual gas components from the mucosal lining (in regions in which these are in good contact with the microcirculation), and 3) by flow of gas through any openings in the tympanic membrane (TM), for example, where this is perforated, or where a ventilation tube (VT) has been inserted. Gas does not pass, physiologically, from or into the ME across an intact TM.¹

While in the normal ME the total pressure is close to atmospheric, and the partial pressures of the component gases add up to this pressure, the partial pressures of the gases dissolved in tissue are determined and maintained by the blood in the microcirculation. Their sum is generally subatmospheric by an amount Δp^* .² In the mucosa, given an adequate blood supply through the microcirculation, the partial pressures of the component gases should thus be at these same physiologic, interstitial tissue values and Δp^* should, there as elsewhere, be about 54 mm Hg.² This 54 mm Hg pressure advantage of ME gas over the mucosal lining is then distributed "algebraically" over the three major gas components — nitrogen (including argon), oxygen, and carbon dioxide — in such a way that a fixed, steady state composition results for the ME gas contents.¹ "Algebraically" means that the individual partial pressure difference (ME to tissue) can be negative as well as positive. Only the sum of these differences has to be positive and equal to 54 mm Hg. Water vapor is in equilibrium with liquid water in tissue and is thus everywhere at its saturated partial pressure value of 47 mm Hg at 37°C.²

The ET, under normal circumstances, alternates

between two states: a state in which it is closed (phase I) and no gas can pass through it, and a state in which it is open (phase II) and a flow of gas can occur. Most of the time the ET is in phase I, and it goes into phase II for only a fraction of a second in response to some maneuver that causes the ET cartilage to be pulled or pushed apart. During phase I, of the long time span Δt_I , during which the ET is closed, the individual gas components can enter or leave the ME only via the mucosa. The direction of component flux depends on the sign of the partial pressure difference.¹ If, in overall terms, gas is absorbed during phase I, the total pressure in the ME will drop. Hence, during phase II, of the very brief time span $\Delta t_{II} \ll \Delta t_I$ during which the ET is open, a bolus of gas from the nasopharynx (NP), and of NP gas composition, will very rapidly enter the ME. If NP pressure is atmospheric and stays constant, a steady state arises that was analyzed in our preliminary publication.¹

It turns out, however, that under normal physiologic conditions NP pressure is not constant, but fluctuates with a period Δt lying between Δt_{II} and Δt_I .³ In consequence, the direction of gas flow through the ET, when it is open, will alternate, and a parameter, the to-and-fro ventilation rate $V\Delta p/\Delta t_I$, has been shown to characterize the individual ear,⁴ where V is the total volume of the ME gas space and $\pm \Delta p/2$ is the variation in NP pressure (with respect to atmospheric). Small $V\Delta p/\Delta t_I$ values correspond to the case discussed preliminarily.¹ Large $V\Delta p/\Delta t_I$ values, however, produce effects that can be far-reaching.⁴

There are several reasons why NP total pressure will fluctuate. Respiratory activity and swallowing cause movement of gas through the NP, and pressure varies accordingly. It becomes positive when

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gas is expired, and negative when gas is inspired. The NP pressure goes from positive to zero to negative and back to positive in a time span of average duration Δt . Furthermore, atmospheric pressure is not constant. It changes with the weather and the altitude. For the NP the pressure level associated with "zero" is thus changing, and an absolute pressure sensor would record a complex pressure history that represents the superposition of all these effects. In phase II, therefore, when the ET is open for the brief time Δt_{II} , the ME space equilibrates, in total pressure, with the level of pressure found in the NP at that instant along with what is a varying absolute pressure record.⁴ Even though phase II occurs at a point in the respiratory cycle at which the pressure change in the NP is minimal,⁵ the pressure on the ME during phase II will never be exactly the same each time. In our estimate it will vary by an amount Δp of at least 1 mm Hg up or down. Hence, when the ET opens next, after the long time span Δt_I , the pressure then prevailing in the NP will be totally unrelated statistically to the pressure that had been "trapped" in the ME on the previous occasion of opening.³ The NP pressure to which the ME is exposed can be either larger or smaller than the pressure in the ME, but will remain roughly constant for the brief 0.5 second of the opening time Δt_{II} ,⁴ which is much shorter than the duration Δt of pressure variation in the NP (some 5 seconds). Hence, only on about half the occasions when the ET opens will a bolus of NP gas enter the ME. On the other occasions a bolus of ME gas will leave it.

These random ventilatory pressure changes, although small, have important effects on the steady state composition in the physiologic ME.⁴ Starting from the case treated earlier,¹ in which the to-and-fro ventilation of the ME, due to pressure changes in the NP, is zero, and in which most of Δp^* goes to increase the partial pressure of nitrogen in the ME,¹ we could show that there is a smooth transition to a case in which to-and-fro ventilation is dominant, in which carbon dioxide, in consequence, is released into the ME, and in which the gas contents of the ME tend to the composition of the gas in the NP.⁴ While in a case of poor to-and-fro ventilation total pressure tends to drop because of overall gas absorption during phase I (ET closed), it will tend to rise, owing to carbon dioxide release, when there is a strong ventilatory flow of gas (sometimes in, sometimes out of the ME) during phase II. The model thus very successfully accounts for the fluctuations in state and response observed with the normal, physiologic ME.⁶

The analysis has to be radically revised, however, when under nonphysiologic conditions a route of permanent access of gas to the ME is provided. Two such cases will be discussed in this paper: the permanently patulous ET⁵ and the ME with a VT inserted in the tympanic membrane.⁷ As pressure

MIDDLE EAR GAS COMPOSITION

	Gas Component, <i>i</i>			
	N ₂	O ₂	CO ₂	H ₂ O
p_i^* (mm Hg)	573	40	46	47
p_i' (mm Hg)	566	120	27	47
p_i^{ur} (mm Hg)	570	143	0	47
α_i/α_{N_2}	1	1.8	34	∞

Data from Loring and Butler² and Ostfeld and Silberberg.⁴

p_i^* — partial pressure of gas *i* in mucosal lining of middle ear, p_i' — partial pressure of gas *i* in nasopharynx, p_i^{ur} — partial pressure of gas *i* in air saturated with water vapor at 37°C, α_i/α_{N_2} — absorption rate of gas *i* by mucosal lining of middle ear in terms of absorption rate of nitrogen.

fluctuates in the NP and/or in the external ear canal, gas is pumped in and out of the ME in some continuous fashion. A steady state can be envisaged, but the conditions to which it is subject are very different.

PERMANENTLY PATULOUS EUSTACHIAN TUBE

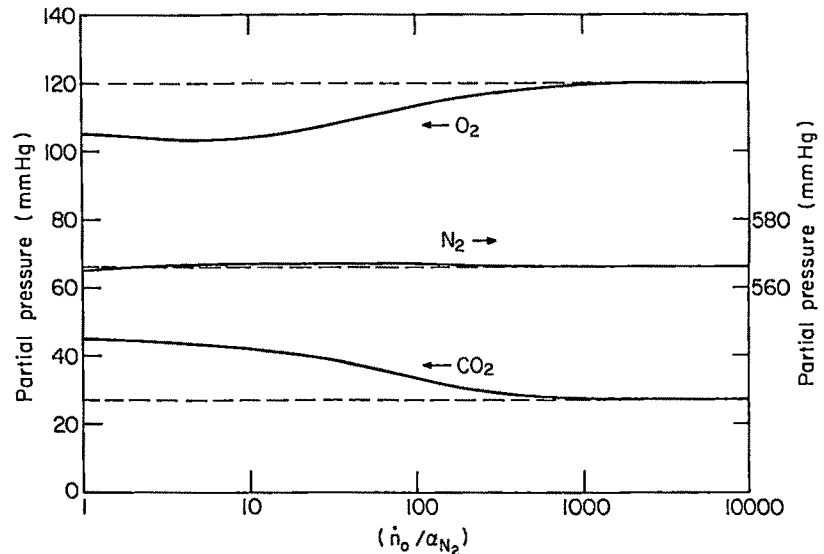
Although the chronically open ET is not a very common occurrence,⁵ its discussion presents some points of interest, since in such a case the pressure fluctuations in the ME tend to match the pressure fluctuations in the NP. The steady state that results in this case is analyzed in Appendix A and the compositions of ME gas derived from equation A7 and the data in the Table^{2,4} are summarized in Fig 1.

Figure 1 gives the partial pressures of nitrogen, oxygen, and carbon dioxide in the ME as a function of the rate of ventilation parameter, $\dot{n}_0/\alpha_{N_2}$, which is the rate of ventilation $\dot{n}_0$ of gas through the ET expressed in units of the gas absorption coefficient α_{N_2} for nitrogen by the mucosa. Figure 1 covers the range from the point at which the ventilation rate $\dot{n}_0$ through the ET is negligibly small ($\dot{n}_0/\alpha_{N_2}$ of the order of 1 or less) to the case in which it is large and $\dot{n}_0/\alpha_{N_2}$ is of the order 10,000.

The gas absorption coefficient α_{N_2} represents the molecular absorption rate of nitrogen by the mucosa when the partial pressure difference of nitrogen between the ME gas space and the mucosa is 1 atmosphere, ie, 760 mm Hg. It can be calculated from the overall gas absorption rate of the mucosa and is found to be 2.8×10^{15} molecules per second.⁴ The units of α_{N_2} are thus molecules per second, the same as those of $\dot{n}_0$, and the parameter $\dot{n}_0/\alpha_{N_2}$ is dimensionless. Its value is about 100 when in the equation A5 in Appendix A for $\dot{n}_0$ we put $\Delta t = 5$ seconds,⁴ $VM = 0.422 \times 10^{-19}$ cm³ per molecule at 37°C, the gas diffusion constant $D = 0.233$ cm²/s at 37°C, and the effective dimensions d_E and L_E of the open ET equaling 0.2 cm and 2 cm, respectively.^{8,9} The remaining factor, Δn , in equation A5, the number of molecules of gas transferred, is calculated from equation A2 by putting atmospheric pressure $p_0 = 760$ mm Hg, the pressure variations in the NP $\Delta p = 1$ mm Hg,⁴ and the volume of the ME $V = 20$ mL.^{1,4}

It will be noted (Fig 1) that nitrogen partial pres-

Fig 1. For patulous eustachian tube: middle ear gas composition in dependence on rate of ventilation, $\dot{n}_o/\alpha N_2$. Dashed lines — nasopharynx gas composition.



sure is at its NP value (and thus slightly below the tissue level) over the entire range of ventilation rates $\dot{n}_o/\alpha N_2$. At high ventilation rates $\dot{n}_o/\alpha N_2$ the gas composition tends to match that in the NP in all respects. At a low $\dot{n}_o/\alpha N_2$, on the other hand, the oxygen partial pressure, although lower, is still much above its value (40 mm Hg) in tissue, whereas carbon dioxide partial pressure tends to match tissue level from below. There exists thus an enhanced potential for oxygen absorption at high ventilation rates $\dot{n}_o/\alpha N_2$, while at the same time carbon dioxide tends to be vented out of the ME through the ET. Total ME pressure, as is obvious, follows that in the NP.

Our estimate of 100 for $\dot{n}_o/\alpha N_2$ occurs somewhere in the middle of Fig 1. Note that only the logarithm, ie, the order of magnitude of the dimensionless ventilation rate parameter $\dot{n}_o/\alpha N_2$, is significant in describing any particular case.

VENTILATION TUBE AND CONVALESCENT EAR

In the case here considered a pathologic ear has been treated by the insertion of a VT into its TM (Fig 2). We shall assume that the ET is functional, ie, opens and closes normally. Any accumulation of effusions and obstruction of the ET that may have

motivated the VT insertion are assumed to have disappeared. We are thus discussing a case in which there are no problems with pressure equalization by muscular opening of the ET.⁷

This case is described and analyzed in Appendix B and the results are presented in Fig 3¹⁰ in terms of the two rate of ventilation parameters $\dot{n}_o T/\alpha N_2$ and $\dot{n}_o E/\alpha N_2$, representing, respectively, the ventilation rates through the VT and the ET, both in units of αN_2 . Note that the ET ventilating activity influences the gas composition only in the region in which VT ventilating activity, $\dot{n}_o T/\alpha N_2$, is small.

On the basis of the Table and if we assume that $d_v = 0.12$ cm, $L_v = 0.1$ cm, $\eta = 1.9 \times 10^{-4}$ poise, $\Delta p = 1$ mm Hg,⁴ $\Delta t_I \approx 10^3$ seconds,³ and $\Delta t_{II} = 0.5$ second,³ and introduce the values for D , V_M , d_E , L_E , and αN_2 already given, we find from equations B6 and B7 that $\dot{n}_o T/\alpha N_2$ is about 220 in this case and that $\dot{n}_o E/\alpha N_2$ is about 100. At $\dot{n}_o T/\alpha N_2$ of about 220 (Fig 3), the ME gas composition in the average ear with an inserted VT is essentially independent of the ET ventilating rate $\dot{n}_o E/\alpha N_2$.

We note that nitrogen partial pressure is identical to that in the atmosphere outside the TM over the

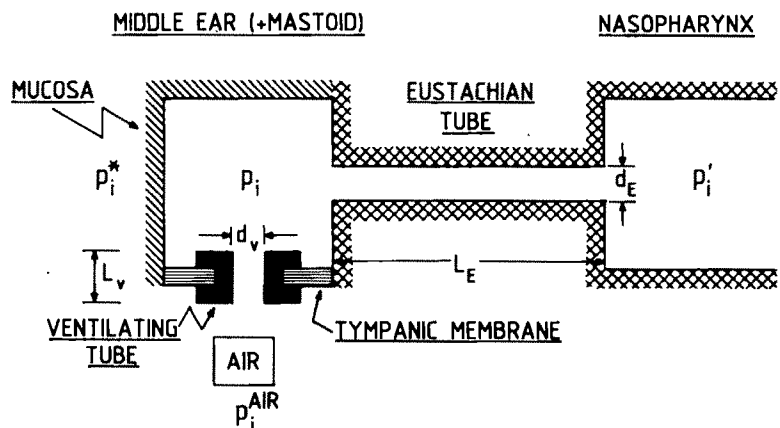


Fig 2. Schematic view of middle ear system showing open eustachian tube and ventilation tube in place. See text for abbreviations.

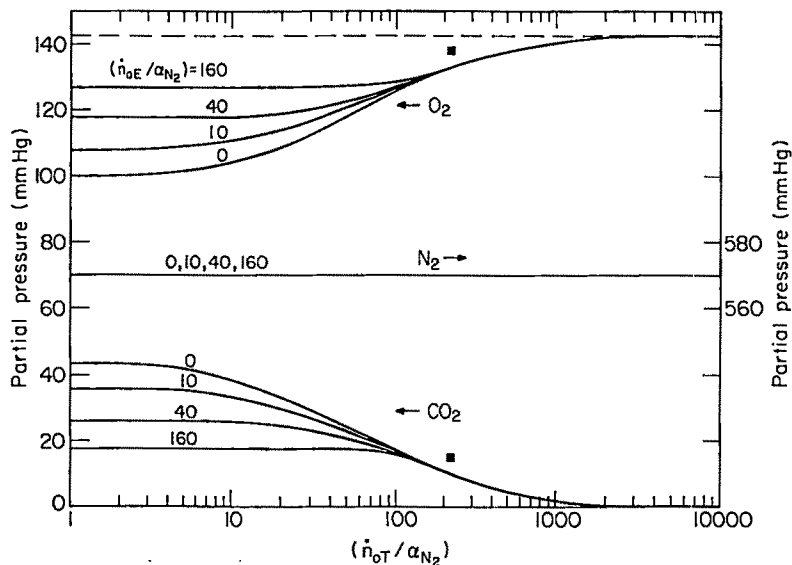


Fig 3. For convalescent middle ear with inserted ventilation tube: middle ear gas composition in dependence on rates of ventilation, $\dot{n}_oT/\alpha_{N_2}$, through ventilation tube, and $\dot{n}_oE/\alpha_{N_2}$, through eustachian tube. Dashed line — PO_2^{AIR} , ■ — data of Felding et al.¹⁰ Note that $PN_2^{AIR} = 570$ mm Hg and $PCO_2^{AIR} = 0$.

entire range, and that as in the case of the patulous ET, the ME vents carbon dioxide into and strongly absorbs oxygen from its gas space when $\dot{n}_oT/\alpha_{N_2}$ is large.

We have found one measurement of gas composition in an ME with an inserted VT and have plotted these data¹⁰ in Fig 3 at the estimated value 220 for $\dot{n}_oT/\alpha_{N_2}$. The comparison with the model calculation is not unreasonable, particularly if it is remembered that the air outside the VT in the external ear canal has been assumed to be fully saturated with water. This may not be the case in practice, and the partial pressures of the other gases, as measured, would thus be correspondingly larger.

DISCUSSION

Large total pressure changes in the NP lead to good ventilation of the ME and thus create an ME gas composition equal to NP gas both with a normally functioning⁴ and a permanently patulous ET. With a VT in place, the composition tends to that of the atmosphere in the external ear canal.

In the normal ME the parameter that numerically "measures" to-and-fro ventilation was shown to be $V\Delta p/\Delta t$.⁴ Here V is the volume of the ME in cubic centimeters, Δp is the magnitude of pressure variation in millimeters of mercury, and Δt is the average length of time between ET openings in minutes. To-and-fro ventilation rate values $V\Delta p/\Delta t$ below 1 indicate that ME pressure tends to be negative and that PN_2 in the ME will be high. Large to-and-fro ventilation rates (large $V\Delta p/\Delta t$ values), on the other hand, produce a strong increase in ME PO_2 , produce a decrease in ME PCO_2 , and lead to positive ME total pressures. Carbon dioxide is thus vented through the ET from the mucosa, while there is enhanced oxygen absorption. Note that if the volume V of the ME (including the mastoid) is large, the extent of to-and-fro ventilation and the

effect on ME gas composition is large. In younger children, in whom the mastoid space is not yet developed and V tends to be small, the to-and-fro ventilation process will thus be poorer.

In the case of a convalescent ear with an inserted VT, a reduced ventilation rate (ie, a smaller $\dot{n}_oT/\alpha_{N_2}$), due, say, to a partially obstructed VT (ie, a smaller dV) causes PO_2 to drop and PCO_2 to rise. A reduced flow through the VT can in part be compensated for by an adequate ventilating flow through the ET. For example, if the ET ventilating rate $\dot{n}_oE/\alpha_{N_2}$ is 100, as we have estimated, ventilation through the VT will ensure a stable ME gas composition for almost any value of the VT ventilating rate $\dot{n}_oT/\alpha_{N_2}$, high or low (Fig 3).

Note that both the ventilation rate parameters and the compositions predicted in Figs 1 and 3 are to be considered averages in comparison with measured data. In other words, one has to collect an abundance of data to see whether the dependence predicted emerges from these results. No individual measurement should be expected to coincide precisely with the curve. The results, even when the same ear is monitored under seemingly constant conditions, must be expected to vary with time.

Note, moreover, that in all the cases discussed it is the logarithm, ie, the order of magnitude of the ventilation rate parameters $V\Delta p/\Delta t$, $\dot{n}_o/\alpha_{N_2}$, $\dot{n}_oT/\alpha_{N_2}$, and $\dot{n}_oE/\alpha_{N_2}$, that strongly affects the composition. Only a rough estimate of these values is thus required in order to classify an ear. This is of considerable advantage, since some of the gas partial pressure values given in the Table are not precisely known. We believe them to be "reasonable estimates,"² but reliable, direct information is not as yet available. Tissue values, in particular, are not easily obtained, and some indirect procedure may eventually have to be employed. With modern means it would, however, not be too difficult to

sample and analyze NP gas directly.

Given that the partial pressure values in tissue (the mucosa) and the NP are known, our analysis has reduced the characterization of the steady state gas composition in the ME to the determination of one, or perhaps two, ventilation rate parameters. Moreover, since only the order of magnitude of these parameters affects the composition, the clinician should, merely by assessing the approximate values of a relatively short list of variables, be able to derive some insight in any particular case. The parameters he or she has to estimate are the ME gas space volume V , which is said to range between 2 and 20 mL; the pressure variation Δp in the NP, which (with no sniffing) can go from 0.4 to well over 10 mm Hg;

the time between ET openings Δt , which is usually as short as several minutes but can be as long as several hours; the effective ET opening width dE , which depends strongly on the individual ET and its state of obstruction; and the diameter of the VT dV , which is generally on the order of 1 mm, but may become partly blocked during convalescence.

Uncommon behavior patterns are not included, but cases of habitual nose blowing or sniffing, for example, differ from the situations so far considered only in the extent of the pressure changes induced in the NP. High Δp values will considerably increase the ventilation rate through the ET and thus induce conditions of increased oxygen absorption by the mucosa and increased carbon dioxide venting from it.

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APPENDIX A: PERMANENTLY PATULOUS EUSTACHIAN TUBE

Schematically, the situation is as illustrated in Fig 2 if, for present purposes, it is assumed that the TM is intact, that the VT shown there does not exist, and that the ET is permanently open.

The balance equation for each component, i , in ME gas, is then given by

$$(A1) \quad -\alpha i(p_i - p_i^*)/p_o + (\Delta n/\Delta t)(p_i' - p_i)/p_o = 0$$

where the parameters in equation A1 have the following definitions: αi is the gas absorption coefficient for component i , the rate at which molecules of gas i are absorbed into the entire area of the ME mucosa, or are released from it, if it is assumed that the applied partial pressure difference is 760 mm Hg; p_i is the partial pressure of gas i in the ME; p_i^* is the partial pressure of gas i in the mucosa; p_i' is the partial pressure of gas i in the NP; p_o is atmospheric pressure; and Δt is the period of the pressure fluctuation in the NP; Δn , if VM is the volume occupied by one molecule of gas at temperature 37°C and overall pressure p_o , is given by

$$(A2) \quad \Delta n = (V/VMp_o)\Delta p$$

and represents the number of molecules of gas, which according to Boyle's law are ventilated, on the average, into or out of the ME (of total volume V) in consequence of a total pressure change Δp . All pressures are expressed in millimeters of mercury.

The first term in equation A1 describes the gas exchange between the mucosa and the ME cavity. The second term deals with ventilation through the ET and takes into account that for half the respiratory cycle time Δt , Δn molecules of gas, composition p_i' , are being pushed into the ME and that for the other half of the cycle time a similar number of molecules of gas, at composition p_i , are being pushed out.

In terms of material balance, however, equation A1 is not complete. In cases in which only small volumes of gas are convected through the ET, a reasonably stable gradient of partial pressures will become established over the length LE of the narrow, open, cartilaginous channel in the patulous ET. In terms of its effect on gas flow this channel can be replaced by the cylinder shown in Fig 2. Along the partial pressure gradient of gas i in this cylinder the molecules of i will diffuse at a rate given by Fick's equation, giving rise to an additional term from this effect, which (in the same units as equation A1) can be written

$$(A3) \quad (\pi dE^2/4LE)(D_i/VM)(p_i' - p_i)/p_o$$

where (see Fig 2) dE is the diameter and LE is the length of the equivalent cylinder that replaces the cartilaginous narrow region in the ET and D_i is the diffusion constant of gas i . We note that the same partial pressure difference as in the second term of equation A1 also occurs in expression A3. Moreover, as in equation A1, so also in A3, the factor multiplying the partial pressure difference will be common to all gas components i , if we replace D_i by a diffusion coefficient D assumed to be the same for all i . On this basis it is possible to write equation A1 in the form

$$(A4) \quad -\alpha i(p_i - p_i^*) + \dot{n}_o(p_i' - p_i) = 0$$

in which the parameter

$$(A5) \quad \dot{n}_o = (\Delta n / \Delta t) + (\pi d E^2 / 4 L E) (D / V M)$$

characterizes the rate of flux of gas by convection or diffusion (or both) through the patulous ET.

Adding $\dot{n}_o(p_i^* - p_i) = 0$ to equation A4 and rearranging gives

$$-\alpha i(p_i - p_i^*) + \dot{n}_o(p_i' - p_i^*) - \dot{n}_o(p_i - p_i^*) = 0$$

ie,

$$(A6) \quad (p_i - p_i^*) = [\dot{n}_o / (\alpha i + \dot{n}_o)] (p_i' - p_i^*)$$

so that we find, dividing both denominator and numerator by αN_2 ,

$$(A7) \quad (p_i - p_i^*) = \frac{(\dot{n}_o / \alpha N_2)}{(\alpha i / \alpha N_2) + (\dot{n}_o / \alpha N_2)} (p_i' - p_i^*)$$

Equation A7 allows the composition p_i of ME gas to be calculated as a function of the parameter $\dot{n}_o / \alpha N_2$ and the data in the Table. The parameter $\dot{n}_o / \alpha N_2$ is a measure of the rate of ventilation through the ET in terms of the rate of absorption and release of nitrogen by the mucosa. Figure 1 gives the result of such a calculation based on the Table for a broad range of values of $\dot{n}_o / \alpha N_2$. Note that the Table is based on literature data^{2,4} and on the assumption that NP gas matches expired air in composition.

For a discussion of any particular case the value of $\dot{n}_o / \alpha N_2$ will have to be assessed. Figure 1, however, depends on the data in the Table only.

APPENDIX B: VENTILATION TUBE IN CONVALESCENT EAR

The situation considered is that illustrated schematically in Fig 2. A VT has been inserted into the TM, the ET is functional, and the Figure shows the ear during the brief interval of time, phase 2, in which the ET is open. It is clear that a VT will only have been inserted in an ear that has exhibited some problem with ME aeration — very often an accumulation of effusions and/or atelectasis. The ear as here described is thus a “convalescent” ear, with restored ET function, but still aerated through the VT.

There is in this case direct contact with the atmosphere, through the external ear canal, at all times. The occasional opening of the ET, as depicted in Fig 2, merely provides an additional, briefly used gas transfer pathway over and above the steady absorption and release of gas from the mucosa and gas convection and diffusion through the VT.

The steady state equation for each gas component i thus involves the following terms: at all times, the term

$$(B1) \quad -\alpha i(p_i - p_i^*) / p_o$$

for gas absorption or release at the mucosa, and the term

$$(B2) \quad -[(\pi d V^2 / 4 L V) (D / V M)] (p_i^{AIR} - p_i) / p_o$$

for Fickian diffusion through the VT. The parameters αi , p_i , p_i^* , D , and $V M$ in B1 and B2 have been defined in Appendix A. In addition, in expression B2, $d V$ is the diameter and $L V$ is the effective length of the VT and p_i^{AIR} represents the partial pressure of gas component i in an atmosphere fully saturated with water at 37°C. Terms B1 and B2 are the only terms operative when the ET is closed.

When the ET opens for the brief interval Δt_{II} , the ME is exposed in addition to the total pressure difference that exists at that instant between the NP and the outside atmosphere. A strong, short-lived flow of gas through the VT will thus occur, and the partial pressure gradient of equation B2 will temporarily be disturbed. Since this disturbance and its aftermath represent only a very brief disruption in a process that goes on steadily for a much longer time, it is reasonable to neglect the effect of this interruption on term B2. Both B1 and B2 are thus considered to be operative at all times.

When the ET opens and a convected flow through the ME is induced, two situations can arise: the total pressure in the NP is larger than atmospheric, or it is smaller than atmospheric. Hence, if Δp is the mean peak-to-peak total pressure change in the NP, the average pressure difference driving gas through the ET will be either plus or minus $\Delta p / 4$. In consequence either a bolus of NP gas enters the ME and simultaneously an equal-size bolus of ME gas leaves via the VT, or a bolus of atmospheric air enters the ME via the VT and an equal-size bolus of ME gas leaves via the ET. If each bolus is of volume $\Delta V = V \Delta p / p_o$ and thus involves $\Delta n = V \Delta p / V M p_o$ molecules, it follows that the change in the contents of gas component i , during a period $2 \Delta t_I$ (ie, for the interval of time containing two episodes of ET opening) will be given by

$$(B3) \quad (\Delta n / 2 \Delta t_I) [(p_i' - p_i) + (p_i^{AIR} - p_i)] / p_o$$

In order to determine Δn we note that the convection flux, $\Delta n / \Delta t_{II}$, of gas through the ET, either into or out of the ME, is given by the Poiseuille equation, which for a tube of diameter d and length L can be written

$$(\Delta n / \Delta t_{II}) V M = (\pi / 8) (d / 2)^4 (\Delta p / L \eta)$$

where η is the viscosity of gas at 37°C and p_o . If, therefore, we can replace the ET by a narrow cylinder of diameter $d E$ and length $L E$, we can write

$$(B4) \quad \Delta n / \Delta t_{II} = (\pi / 128) (d E^4 \Delta p / L E \eta) / V M$$

The steady state equation, putting B1, B2, and B3 together and multiplying by p_o , thus becomes

$$(B5) \quad -\alpha i(p_i - p_i^*) + \dot{n}_o T (p_i^{AIR} - p_i) + \dot{n}_o E (p_i' - p_i) + \dot{n}_o E (p_i^{AIR} - p_i) = 0$$

We now add

$$(\dot{n}_o T + 2 \dot{n}_o E) (p_i^* - p_i^*) = 0$$

to equation B5, which thereby becomes

$$-\alpha i(p_i - p_i^*) - \dot{n}_o T (p_i - p_i^*) - 2 \dot{n}_o E (p_i - p_i^*) + (\dot{n}_o T + \dot{n}_o E) (p_i^{AIR} - p_i^*) + \dot{n}_o E (p_i' - p_i^*) = 0$$

where

$$(B6) \quad \dot{n}_o T = (\pi d V^2 / 4 L V) (D / V M)$$

and

$$(B7) \quad \dot{n}oE = (\pi/256)[dE^4/LE](\Delta p/\eta VM)(\Delta t\Pi/\Delta tI)$$

are the gas ventilation rates through the VT and the ET, respectively. Rearranging and dividing by $\alpha i + \dot{n}oT + 2\dot{n}oE$ then gives

$$(B8) \quad p_i - p_i^* = \frac{\dot{n}oT + \dot{n}oE}{\alpha i + \dot{n}oT + 2\dot{n}oE} (p_i^{AIR} - p_i^*) + \frac{\dot{n}oE}{\alpha i + \dot{n}oT + 2\dot{n}oE} (p_i' - p_i^*)$$

We now define the dimensionless numbers

$$(B9) \quad yT = (\dot{n}oT/\alpha N2)$$

and

$$(B10) \quad yE = (\dot{n}oE/\alpha N2)$$

and find that B8 can also be expressed as follows:

$$(B11) \quad (p_i - p_i^*) = \frac{(yT + yE)(p_i^{AIR} - p_i^*) + yE(p_i' - p_i^*)}{[\alpha i/\alpha N2] + yT + 2yE}$$

The composition p_i of ME gas is thus a function of the dimensionless parameters $yT = (\dot{n}oT/\alpha N2)$ and $yE = (\dot{n}oE/\alpha N2)$ and depends on the data in the Table only. Figure 3 gives the results.

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SEATTLE, WASHINGTON

PATIENT

A 26-year-old man fell on a sharp stick while running through a wooded area and impaled his right cheek. On evaluation in the emergency trauma center the patient was awake and lucid with stable vital signs. His voice was hoarse. Examination revealed the palpable end of a stick in his right cheek just protruding through the skin. His tongue deviated to the right and the palate elevated asymmetrically. There was no mass in the parapharyngeal space and no evidence of hematoma in the neck. The trapezius and sternocleidomastoid muscles were weak on the right. Indirect and fiberoptic examination of the larynx documented a right true vocal cord palsy. Horner's syndrome of the right eye was evident. The remainder of the findings on his neurologic evaluation were normal and nonfocal.

RADIOGRAPHIC FINDINGS

Computed tomography (CT) was performed to evaluate the path of the stick (see Figure, A). The emergency CT scan obtained with contrast revealed the wooden stick as a gas-density structure. This would imply that the stick was old and dried out, since a piece of live green wood would be closer to soft tissue or water density. While conventional axial CT images document the location of the stick, the use of reformatting in the parasagittal plane parallel to the long axis of the stick gives a dramatic image of the depth of the penetration.

Computed tomographic images also indicated sigmoid sinus thrombosis¹⁻³ and internal carotid artery compression. Angiography confirmed compression and/or thrombosis of the internal carotid artery and documented intact collateral circulation distal to the occlusion via the circle of Willis. In addition, it confirmed internal jugular and sigmoid sinus thrombosis. In this case (see Figure, B), the tapered appearance of the midcervical internal carotid artery suggested that an intimal flap had developed, causing occlusion.

MANAGEMENT

The patient was taken to the operating room,

where a combined intracranial-extracranial procedure was undertaken. A craniotomy was done to ligate the carotid artery within the carotid canal in the petrous bone. A cortical mastoidectomy was then performed and the sigmoid sinus exposed low in the mastoid. The sinus was packed with fascia and muscle. The neck was opened, the jugular vein ligated, and the internal carotid artery ligated distal to the bifurcation. A cervicofacial flap was elevated to expose the piece of wood, which was extracted without difficulty (see Figure, C). No bleeding was encountered with extraction of the stick.

The patient recovered uneventfully. Findings on neurologic examination were unchanged; the patient was left with a complete right-sided palsy of cranial nerves IX, X, XI, and XII and a right-sided Horner's syndrome. Gelfoam injection of the right vocal cord was performed 2 weeks after injury to control aspiration and improve his voice. Laryngeal electromyography 6 weeks after injury failed to document any evidence of reinnervation. A thyroplasty was eventually performed to medialize the right cord; it resulted in improved vocal quality and a stronger cough.

DISCUSSION

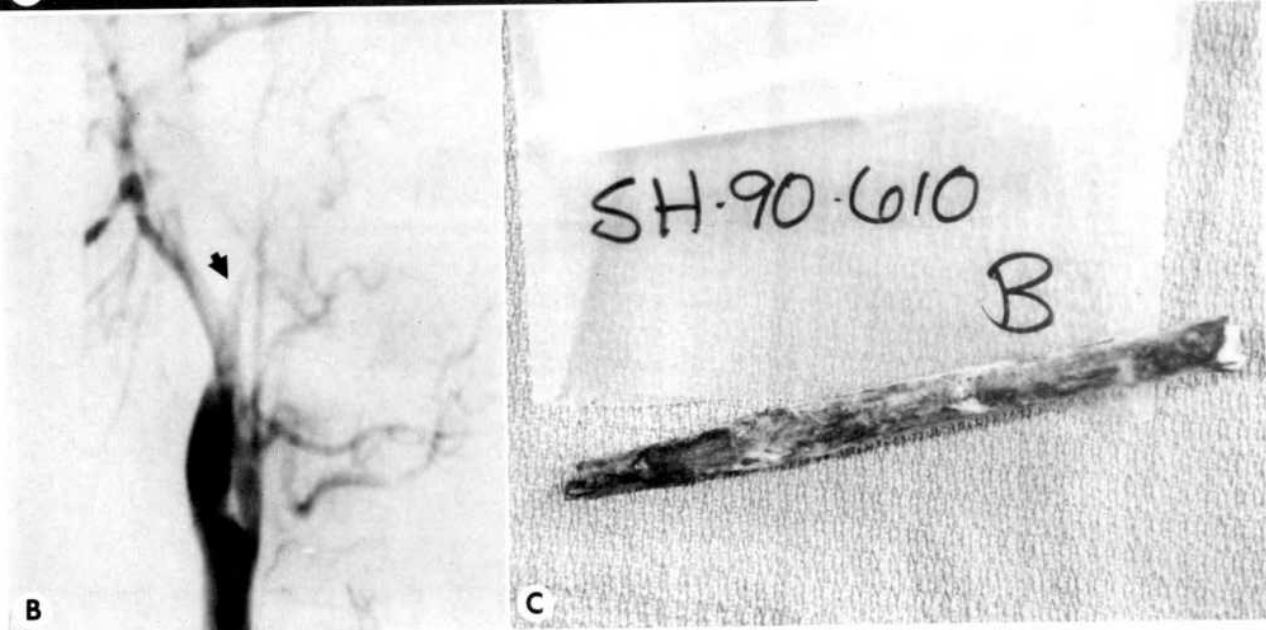
Paralysis of the cranial nerves exiting from the skull base is most commonly the result of a primary neoplasm (neurilemmoma or glomus tumor) involving the jugular foramen. Vernet's syndrome consists of paralysis of the cranial nerves that pass through the jugular foramen (cranial nerves IX, X, and XI).⁴ Penetrating trauma is a relatively rare cause of jugular foramen syndrome. This patient had deficits resulting from paralysis of cranial nerves IX, X, XI, and XII, as well as the sympathetic nerve fibers. Villaret's syndrome is the eponym for the constellation of neurologic deficits in this patient.

The surgical planning prior to removal of the stick from the jugular foramen was intended to minimize the possibility of uncontrolled bleeding upon extraction. Proximal venous control was obtained by ligation of the jugular vein in the neck, and distal control by exposing the sigmoid sinus low

From the Skull Base Center (all authors) and the Departments of Otolaryngology-Head and Neck Surgery (Overholt, Weymuller), Radiology (Dalley), and Neurological Surgery (Dalley, Winn), University of Washington, Seattle, Washington.



Penetrating trauma of jugular foramen. A) Parasagittal reformatted computed tomographic scan with intravenous contrast demonstrates black gas-density linear structure representing dry wooden stick extending from oral cavity posteriorly and superiorly through right jugular foramen (arrow). Tip of stick projects into right cerebellopontine angle cistern. B) Lateral right common carotid angiogram shows smooth, tapered occlusion of right internal carotid artery 4 cm distal to carotid bifurcation (arrow). Wooden stick within jugular foramen has compromised adjacent cervical internal carotid artery secondary to intimal dissection originating at level at which artery entered vertical portion of carotid canal. Sigmoid sinus was also partially thrombosed (not shown). C) Wooden stick removed intraoperatively.



in the mastoid and packing fascia deep into the jugular bulb. The only major venous tributary not accounted for was the inferior petrosal sinus, which enters the jugular bulb anteromedially. If significant bleeding occurred upon removal of the stick, it would have been controlled by packing directly through the exposure obtained from each end of the jugular bulb. A similar approach to controlling venous bleeding in a case of traumatic jugular foramen syndrome resulting from a gunshot wound has been described previously.⁵ Arterial bleeding was

controlled proximally by ligation of the internal carotid artery just distal to the bifurcation. Distal control was obtained by ligating the carotid artery within the carotid canal in the petrous bone and prevented retrograde arterial bleeding. This combined approach resulted in minimal blood loss when the stick was extracted from the patient. Ligation of the carotid artery in the petrous bone should also prevent the potential late complication of an aneurysm or arteriovenous fistula.

The reformatted CT scan in the parasagittal

plane was clearly beneficial in this case, as are CT scans in general in the evaluation of facial trauma.⁶ Angiography also added critical information for preoperative planning and should be obtained in

the setting of penetrating trauma above the angle of the mandible (zone III). It should also be considered in any trauma associated with multiple ipsilateral lower cranial nerve deficits.

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PATHOLOGY CONSULTATION

ANGIOLITHIASIS AND SIALOLITHIASIS IN THE HEAD AND NECK

A. KEVIN RAYMOND, MD

JOHN G. BATSAKIS, MD

HOUSTON, TEXAS

Of the two principal forms of macrolithiasis and microlithiasis in the head and neck, that occurring in salivary glands (sialoliths) is much more prevalent than intravascular lithiasis (angioliths). Sialoliths are also more often symptomatic, particularly when formed in the preponderant gland of involvement, the submandibular gland. Angiolithiasis is always coincidental with vascular stasis: in hemangiomas or varices. Both forms of lithiasis share several radiographic features and have a similar basis of formation. For sialoliths, secretory stasis forms a nidus for mineralization. Thrombus formation in vessels is the formative "nucleus" for an angiolith.

Lithiasis (calculi), most often intraluminal, in the head and neck occurs in two forms: sialolithiasis and angiolithiasis. The former is much more common and is exclusively salivary; the latter is vascular-based, sometimes salivary, but more often in oral or perioral soft tissues. Salivary calculi are usually diagnosed by their clinical and radiographic findings. Angioliths may be asymptomatic, are often incidental findings, and can be clinically mistaken for sialoliths. An assessment of these two forms of head and neck calculi follows.

ANGIOLITHIASIS

By definition, an angiolith is a calcified thrombus within venules, veins, or sinusoidal vessels of a hemangioma. The head and neck ranks a very distant second in frequency to pelvic veins for angiolithiasis (phleboliths).¹ In the elderly, oral and perioral phleboliths are usually solitary and found within local varices. In young adults, angioliths may be the only residua of a childhood hemangioma, and in children their presence is very suggestive of a hemangioma, particularly cavernous, either in the parotid gland or in soft tissues of the head and neck.¹⁻³ Angiolithiasis may also occasionally be a feature of syndromes such as Maffucci, Klippel-Trenaunay-Weber, Sturge-Weber, and rubber-bleb nevus syndromes.^{1,2}

The microliths, on radiographs, are small round or ovoid radiopacities.⁴ They are either uniformly radiopaque or show concentric laminations of radiopaque and radiolucent zones. Laminations of alternating high and low mineral content also characterize the histologic appearance of the angioliths (see Figure, A).

Infrared spectrometric and x-ray diffraction tech-

niques indicate the mineralized microlith contains crystals of apatite with calcium phosphate and carbonate salts, and magnesium ammonium phosphate.^{2,3} These findings are consistent with the proposed origin of the vascular calculi that postulates a beginning with organization of a thrombus, secondary mineralization, and progressive enlargement.^{1,3,4}

SIALOLITHIASIS

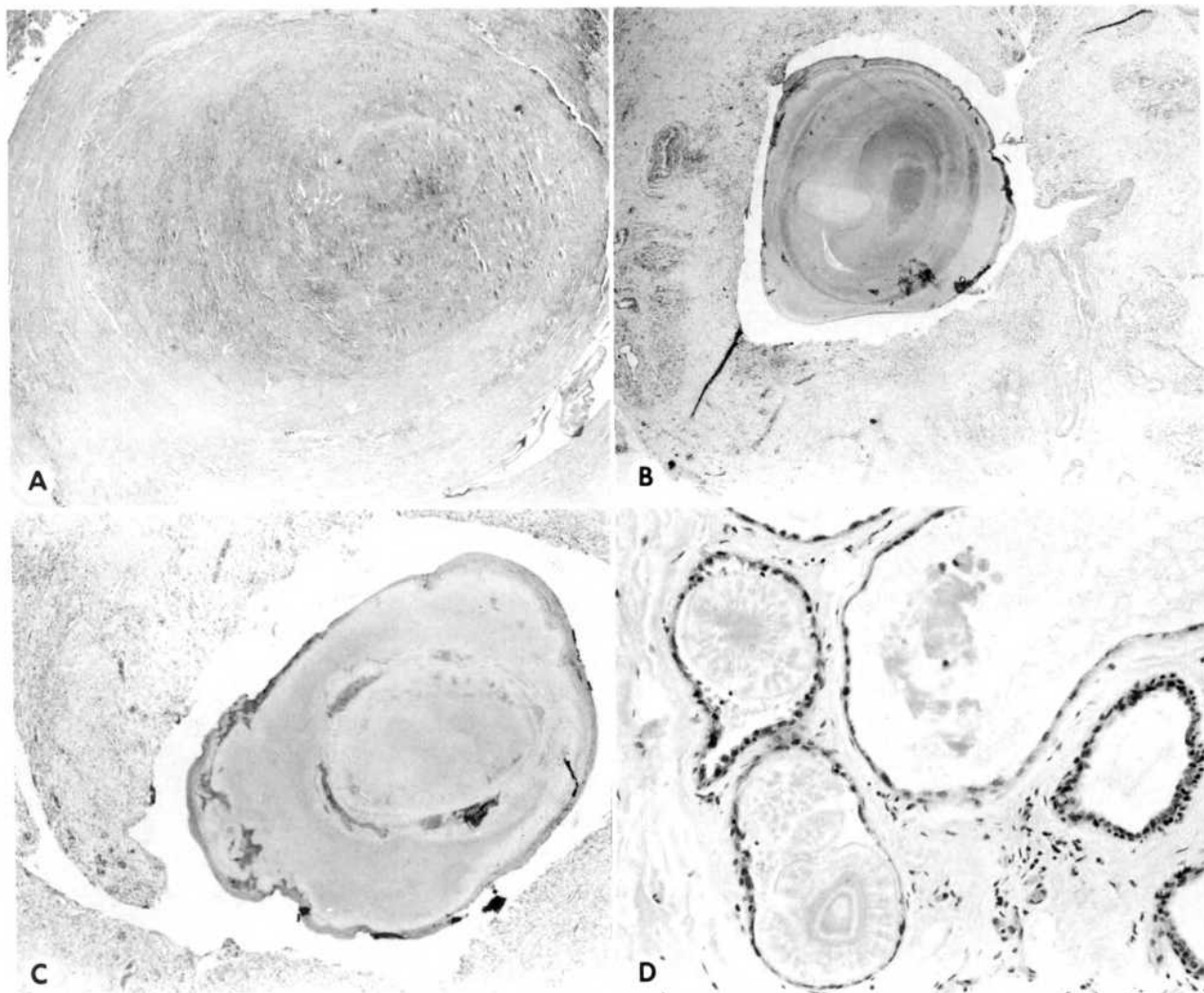
Formation of an intraductal organic gel matrix is the initiating step in the making of a sialolith.^{4,5} Inorganic material (mineralization) is then deposited in the gel to produce the calculus. There is a varying content of organic and inorganic constituents between sialoliths and also within a single calculus. Inspissated mucus (glycoproteins, mucopolysaccharides), lipids, and cellular debris make up most of the organic material.⁵ Calcium salts, particularly phosphates and carbonates, are the principal inorganics.

The typical sialolith is round or oval and manifests alternating organic and inorganic lamellae arrayed around a usually mineralized nucleus. Collagen fibers and metaplastic squamous epithelial cells can be found on the surface of most sialoliths.⁵

Sialolithiasis is most often uniglandular, with the calculi found mainly in the excretory duct part of the salivary duct unit in adults.^{5,6} Intraparenchymal sialoliths are unusual and often are asymptomatic. Any salivary gland can be the site of origin, but the submandibular gland is by far the preponderant gland. In a review of 1,200 major salivary gland cases, 83% of sialoliths were in the submandibular gland, 10% in the parotid gland, and 7% in the sublingual gland.⁵ The frequency of minor salivary gland involvement is not known. Sialoliths are, however, most often seen in the salivary tissues of the upper lip and buccal

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Lithiasis. A) Angiolith in dilated venous space from clinically occult buccal hemangioma in 13-year-old girl (H & E, original x120). Note lamellar arrangement of angiolith around central nidus. B) Sialolith in ectatic duct of minor salivary gland of upper lip (H & E, original x60). Erosion and squamous metaplasia of ductal epithelium is evident, as is chronic sialadenitis of minor salivary tissue. C) Same sialolith shown in B surrounded by granulation tissue of eroded excretory duct (H & E, original x100). D) Polycystic (dysgenetic) disease of parotid gland with laminated sialoliths (H & E, original x180).

mucosa (see Figure; B,C).

Predilection for origin within the submandibular gland is explicable on the basis of that gland's viscous, mucus-rich saliva and the sinuous, bending course of its main duct.^{5,6} A ratio of extraglandular to intraglandular submandibular calculi is given as 7:3 by Rauch.⁶ The ratio is considerably different for the parotid gland, for which there is an estimated ratio of 1:35 for intraglandular and extraglandular occurrences.⁵ We agree with Seifert et al⁵ that the ratio may be too high, but cannot agree with Suleiman et al⁷ that sialolithiasis is the most common cause of recurrent unilateral parotid swelling.

The consequences of salivary calculi are obtained from their ductal obstructions. Recurrent bouts of tender glandular swelling, especially during meals with their secretory stimulation, are typical. If the

obstruction is not relieved, chronic obstructive sialadenitis follows. Because of their larger size and location, submandibular gland sialoliths may be palpated (especially if close to the ostium of the duct or in its middle third). Radiographic examination is diagnostically effective for calculi at the duct's bending point, but is less contributory for intraparenchymal sialoliths. Radiographic examination is of more importance in parotid gland sialoliths, because they are less likely to be palpable.

Surgical treatment for submandibular and parotid duct calculi depends on the accessibility of the calculus. If it is near the ostium of the duct, removal from the duct may be feasible.⁵ In other instances, removal of the affected gland is necessary.⁵

Microlithiasis can also be found in salivary gland neoplasms, most notably in acinic cell and mucoepi-

DISTINGUISHING CHARACTERISTICS OF SIALOLITHIASIS AND ANGIOLITHIASIS

	<i>Sialoliths</i>	<i>Angioliths</i>
Site	Any salivary gland, preponderantly submandibular and uniglandular	Parotid gland and oral perioral soft tissues
Radiographic features	Usually uniformly radiopaque; can be laminated, especially if in main duct of submandibular gland Sialograms show filling defect at site of calculus in duct system	Usually laminated with radiopaque center; can be uniformly opaque if small Sialograms show angioliths external to duct system
Shape and size	Shaped by duct; microscopic to 1 to 2 cm, depending on involved duct or parenchyma	Usually circular to ovoid and usually microscopic to 0.5 cm
Pathogenesis	Duct stasis with increased viscosity forming nidus and secondary mineralization	Intravascular thrombus with secondary mineralization
Associated lesions	Chronic obstructive sialadenitis; polycystic (dysgenesis) disease of parotid gland; neoplasms, particularly acinic cell and mucoepidermoid carcinomas	Hemangiomas, particularly cavernous types; varices with thrombosis

dermoid carcinomas. In these instances, they assume a calcospherite or "psammoma body" configuration and distribution. Their genesis is like that of sialoliths. Polycystic (dysgenetic) disease of the parotid gland characteristically contains microliths within the malformed ducts. In their premineralized or early miner-

alized state (see Figure, D) they allow excellent visual appreciation of the formation of the microcalculi.

The Table compares several characteristics of sialoliths and angioliths.

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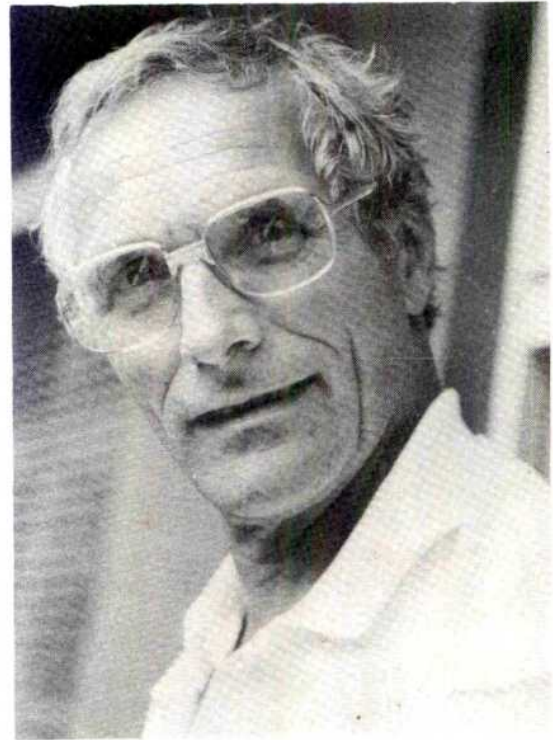
HEINRICH HANS SPOENDLIN, 1927-1991

Henry Spoendlin was one of the outstanding otolaryngologic clinician-investigators of the last half of the 20th century. Arising in one of the great optimistic eras that infrequently occur, he had the foresight, drive, and talent to seize its opportunities.

Henry was born in Zurich, Switzerland, and educated at the Universities of Zurich and Geneva and at the Sorbonne. After many years on the faculty at Zurich, he became professor and head of otolaryngology at the University of Innsbruck in 1976, where he remained until his death from a soft tissue sarcoma. He was a member of innumerable otolaryngologic societies both here and abroad, and the recipient of many awards and honors. His bibliography is extensive and eclectic, much of it significant.

Dr Spoendlin traveled widely and presented papers in the United States frequently. He worked with Harold Schuknecht for an extended period at Harvard. Thus, he was well-known in American medical circles as well as in Europe. Those who knew him personally enjoyed this big, handsome, charming man and respected his considerable talent and achievements.

As biological transmission electron microscopy developed in the 1950s, Dr Spoendlin became proficient in this technology for application in cochlear research. He enjoyed a long and significant career in this chosen area of work, most significantly in his discovery that the vast majority of afferent nerve fibers from the cochlea arise from the inner, not the outer hair cells. These experiments were much doubted when first reported, but were soon con-



firmed. This work profoundly influenced our concepts of hearing mechanisms.

Henry is survived by his wife Marguerite, son Daniel, and daughter Catherine and two grandchildren. His family and friends will miss this most wonderful physician and scientist.

Arndt J. Duvall III, MD

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PATHOLOGY CONSULTATION**Epithelial-Myoepithelial Carcinoma of Salivary Glands**

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INSTRUCTIONS TO AUTHORS

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LABYRINTHINE ENHANCEMENT ON GADOLINIUM-ENHANCED MAGNETIC RESONANCE IMAGING IN SUDDEN DEAFNESS AND VERTIGO: CORRELATION WITH AUDIOLOGIC AND ELECTRONYSTAGMOGRAPHIC STUDIES

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Sudden deafness with or without vertigo presents a difficult diagnostic problem. This article describes 12 patients with enhancement of the cochlea and/or vestibule on gadolinium-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (MRI), correlating the enhancement with the auditory and vestibular function. All patients were studied with T2-weighted axial images taken through the whole brain, enhanced 3-mm axial T1-weighted images taken through the temporal bone, and enhanced T1-weighted sagittal images taken through the whole brain. Cochlear enhancement on the side of hearing loss was found in all the patients. The vestibular enhancement correlated with both subjective vestibular symptoms and objective measures of vestibular function on electronystagmography. In 2 patients, the resolution of symptoms 4 to 6 months later correlated with resolution of the enhancement on MRI. No labyrinthine enhancement was seen in a series of 30 control patients studied with the same MRI protocol. Labyrinthine enhancement in patients with auditory and vestibular symptoms is a new finding and is indicative of labyrinthine disease. While abnormalities on electronystagmograms and audiograms are nonspecific and only indicate a sensorineural problem, enhanced MRI may separate patients with retrocochlear lesions, such as acoustic neuromas, from those in whom the abnormal process is in the labyrinth or the brain.

KEY WORDS — gadolinium, labyrinthitis, magnetic resonance imaging, sudden deafness, vertigo.

INTRODUCTION

Sudden deafness with or without vertigo has long presented a difficult diagnostic problem for clinicians. The evaluation of these patients has evolved to include not only audiologic and vestibular testing but also computed tomography and, most recently, magnetic resonance imaging (MRI) with or without gadolinium. To date, the primary role of MRI in this setting has been to exclude cerebellopontine angle and brain lesions.^{1,2}

Recently we reported labyrinthine enhancement on gadolinium-diethylenetriamine pentaacetic acid-enhanced MRI in five patients with sudden deafness and/or vertigo,³ and correlated them with objective measures of auditory and vestibular function by audiologic and electronystagmography (ENG) studies, respectively.

The purpose of this report is to present seven additional patients with enhancement of the cochlea and/or vestibule and describe further correlation between the level of enhancement in the cochlea and the frequency range of the hearing loss.

MATERIALS AND METHODS

Twelve patients with hearing loss and/or vertigo and gadolinium enhancement of the cochlea and/or vestibule were included in the study. Five of these patients have been previously reported.³ All patients were studied with T2-weighted axial images of the whole brain and with gadolinium-enhanced 3-mm-thick axial T1-weighted images of the temporal bone. The seven most recent patients also had pregadolinium axial T1-weighted images with thin sections taken through the temporal bone. In addition to the clinical information, audiologic studies were available for review in nine patients. Electronystagmographic findings were available in five patients. Viral titers during acute and convalescent phases of the illness were obtained in two patients. Thirty asymptomatic control patients and six patients with acoustic neuromas were also studied with a similar technique.³

RESULTS

In all patients with sudden deafness, cochlear enhancement was present on the symptomatic side (Figs 1-7³). In 1 patient with bilateral sudden deafness, the enhancement was present only in the ear

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Fig 1. T1-weighted, gadolinium-enhanced magnetic resonance image from 73-year-old woman with right-sided hearing loss and vertigo following viral illness. Shows enhancement of right cochlea (solid arrow) and vestibule (open arrow). No enhancement is seen on opposite side. (Reprinted with permission.³)

with the most severe symptoms (Fig 3). In 4 patients with sudden deafness and no vertigo, isolated enhancement of certain segments of the cochlea could be identified. In 3 patients the enhancement was limited to the basal turn of the cochlea. Two of these patients had complete hearing loss, and the third patient had hearing loss limited to the high frequencies only (Fig 5). A fourth patient had enhancement limited to the middle and apical turns of the cochlea. An audiogram revealed middle- and low-frequency hearing loss. In 2 patients, enhancement of the semicircular canals was noted (Fig 7) in addition to the enhancement of the cochlea and the vestibule. The cause of the enhancement of the labyrinth was luetic labyrinthitis in 2 patients, postmumps and postrubella labyrinthitis in 1 patient each, presumed viral labyrinthitis from other viruses in 7 other patients, and bacterial laby-

rinthitis in 1 patient (Fig 6). Six of the 12 patients also had vertigo; however, vestibular enhancement was seen only in 5 patients who had severe ENG abnormalities. One patient with vertigo and no enhancement of the vestibule had only mild ENG abnormalities (Fig 4A). No enhancement of the asymptomatic labyrinth was seen in the 30 control patients. None of the 6 patients with acoustic neuromas had labyrinthine enhancement on the symptomatic side either. The T2-weighted images showed no brain stem abnormalities.

CASE REPORTS

Case 1. A 71-year-old man complained of the sudden onset of vertigo and left-sided hearing loss and tinnitus associated with an influenzalike illness. There was moderate to severe hearing loss on the left (speech reception threshold [SRT] 50 dB) with very poor speech discrimination of 12%. The PBmax was 12% at 90 dB. While the patient had bilateral high-frequency hearing loss, a common finding in the older population, his SRT (14 dB) and discrimination (92%) on the right were normal. There was no response to caloric stimulation of the left ear—a 100% reduction in response. Gadolinium-enhanced MRI (Fig 2A) revealed enhancement of the left cochlea and vestibule, compared with no enhancement on the contralateral side.

A repeat audiogram done 6 weeks after the initial audiogram showed improved hearing with an SRT of 32 dB, discrimination of 52% at 62 dB, and a PBmax



Fig 2. (Case 1) T1-weighted, gadolinium-enhanced magnetic resonance images. (Reprinted with permission.³) A) Initial study, at time of abnormal cochlear and vestibular function in left ear, shows enhancement of left cochlea (solid arrow) and vestibule (open arrow). No enhancement is seen on contralateral side. B) One month after initial study, at which time patient had some improvement in hearing and slight improvement on electronystagmography. There is persistent labyrinthine enhancement. C) Five months after initial study, at which time patient had marked improvement in hearing and resolution of vestibular symptoms. Previously noted enhancement of left cochlea and vestibule is no longer present.

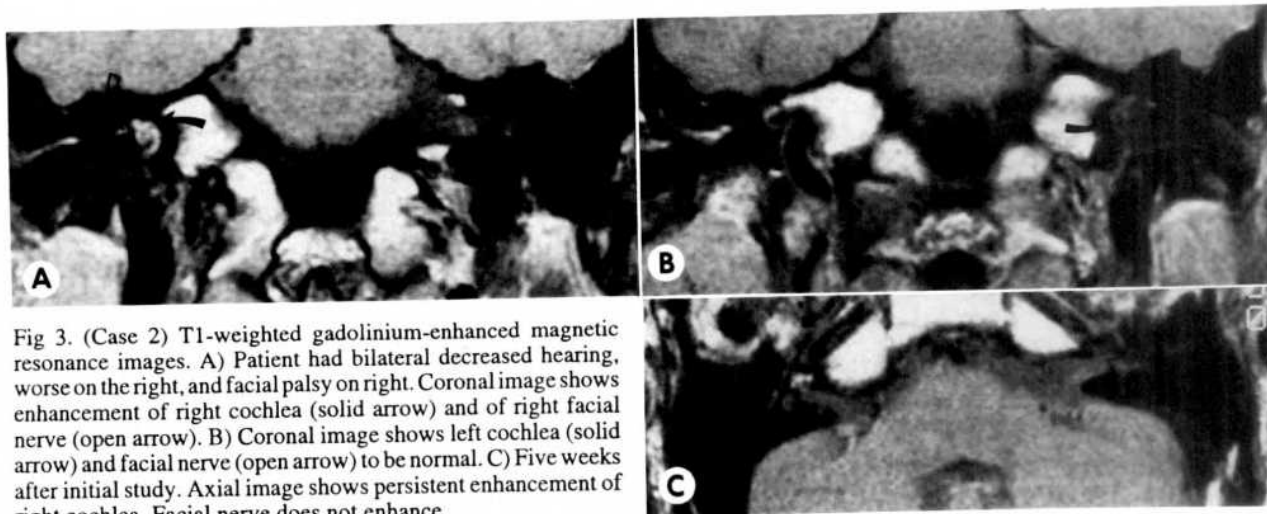


Fig 3. (Case 2) T1-weighted gadolinium-enhanced magnetic resonance images. A) Patient had bilateral decreased hearing, worse on the right, and facial palsy on right. Coronal image shows enhancement of right cochlea (solid arrow) and of right facial nerve (open arrow). B) Coronal image shows left cochlea (solid arrow) and facial nerve (open arrow) to be normal. C) Five weeks after initial study. Axial image shows persistent enhancement of right cochlea. Facial nerve does not enhance.

of 68% at 80 dB. The patient still complained of dizziness requiring meclizine hydrochloride. Repeat ENG still yielded markedly abnormal findings, although slightly improved, with response to calorics on the left 78% lower than on the right. Repeat enhanced MRI done at this time showed persistent enhancement of the left cochlea and vestibule (Fig 2B).

A follow-up audiogram done 5 months after the initial study showed continued improvement in hearing in the left ear with an SRT of 25 dB, discrimination of 48% at 55 dB, and PBmax improved to 88% at 80 dB. The patient's dizziness had resolved completely. A follow-up enhanced MRI done 1 month after the last audiogram (5 months after the initial study) showed no enhancement of either the left cochlea or the left vestibule (Fig 2C).

Case 2. A 39-year-old man experienced sudden bilateral deafness, more severe on the right, and a peripheral right facial paresis shortly after an influenzalike illness. He had no dizziness. An audiogram

revealed marked hearing loss in the right ear, and ENG yielded normal findings. Enhanced MRI (Fig 3A) revealed enhancement of the right cochlea and facial nerve. There was no enhancement of the right vestibule or of the contralateral labyrinth (Fig 3B). The patient had positive fluorescent treponemal antibody absorption in the blood and cerebrospinal fluid. Enhanced MRI (Fig 3C) 1 month after treatment with penicillin revealed persistent enhancement of the cochlea and resolution of the facial nerve enhancement, correlating with persistent hearing loss on the right and resolution of the facial palsy.

Case 3. A 67-year-old woman presented with acute onset of hearing loss and tinnitus on the right, as well as dizziness. She had had a recent influenzalike illness. There was a severe to profound sensorineural hearing loss in the right ear (speech awareness threshold of 65 dB) with 0% speech discrimination. Her SRT (10 dB) and discrimination (100%) on the left were normal. She had only mildly abnormal results on ENG, with a 34% decrease in response to calorics on the right. A decrease of up to 30% is considered

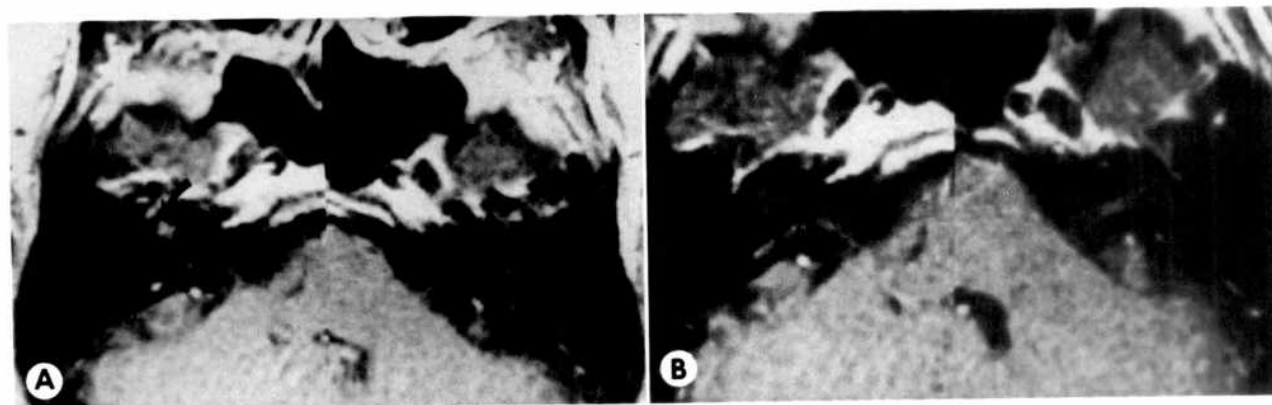


Fig 4. (Case 3) T1-weighted, gadolinium-enhanced magnetic resonance images. A) Initial study, at time of right-sided hearing loss and vertigo with minimally abnormal electronystagmographic findings, shows enhancement of cochlea (solid arrow) but not vestibule (open arrow) on right side. There is no enhancement of asymptomatic side. B) Six months after initial study, at which time patient had improvement in hearing and discrimination. Previously noted enhancement of right cochlea is no longer present.



Fig 5. (Case 4) Axial T1-weighted magnetic resonance images. A) Pregadolinium, demonstrating normal left cochlea (arrow). B) Postgadolinium, at same level. Notice enhancement of basal turn (arrow) but not of apical turn of left cochlea, correlating with patient's high-frequency hearing loss. C) Postgadolinium, through right labyrinth. No enhancement is demonstrated on asymptomatic side.

within normal limits. In addition, there was a significant (13/s) left-beating spontaneous nystagmus. Enhanced MRI (Fig 4A) demonstrated enhancement of the cochlea, but not of the vestibule, on the right side. The other side was normal.

An audiogram done 6 months after the initial study revealed improvement in hearing in the right ear to an SRT of 30 dB, with discrimination improved from 0% to 48%. No enhancement of the labyrinth was present on a follow-up MRI (Fig 4B) done at the time of the repeat audiogram.

Case 4. A 40-year-old woman presented with a 3-week history of left-sided hearing loss. An audiogram revealed a high-frequency hearing loss only. She denied any vertigo. Precontrast T1-weighted MRI revealed normal findings. The postcontrast study demonstrated enhancement of the basal turn of the left cochlea (Fig 5). No enhancement was noted in the apical turn.

Case 5. A 40-year-old man developed pain in the left ear. Fluid was seen on examination behind the left tympanic membrane. The next day the patient devel-

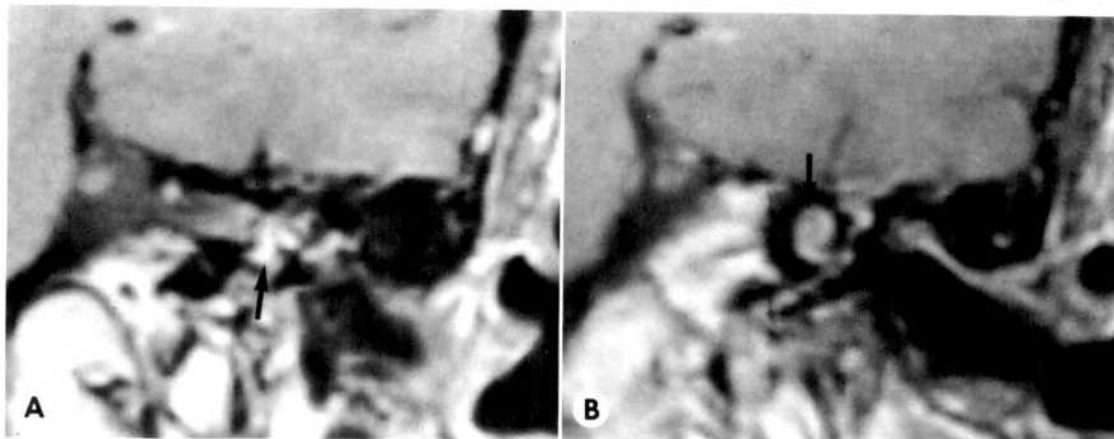


Fig 6. (Case 5) Coronal T1-weighted, gadolinium-enhanced magnetic resonance images. A) Through left internal auditory canal. Notice enhancement of basal turn of cochlea (arrow) and of horizontal segment of left facial nerve. Enhancement of mucosa in middle ear is also seen. B) Three millimeters anterior to section in A. Notice enhancement of middle and apical turns of cochlea (arrow) and of genu of left facial nerve. (Courtesy of Dr C. J. Schatz, Los Angeles, Calif.)

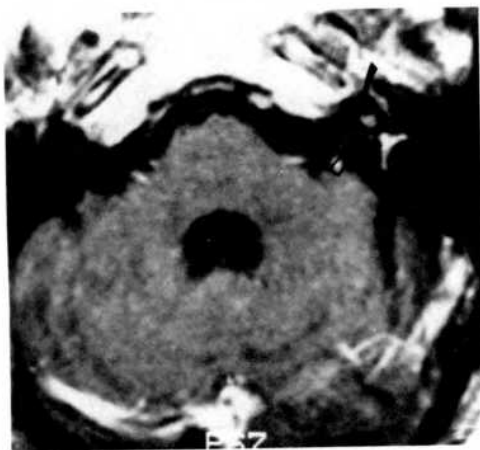


Fig 7. Axial T1-weighted, gadolinium-enhanced magnetic resonance image from 40-year-old woman with left-sided sudden hearing loss and vertigo following upper respiratory tract infection. Notice enhancement of left cochlea (solid arrow), vestibule (open arrow), and part of horizontal and posterior semicircular canals. (Courtesy of Dr Manjul Shah, Cleveland, Ohio.)

opened sudden sensorineural hearing loss and left-sided facial palsy. An MRI demonstrated enhancement of the left cochlea, vestibule, and horizontal segment of the facial nerve (Fig 6). Minimal fluid was seen in the middle ear and mastoid. The patient's pain improved on antibiotics but the hearing loss persisted.

DISCUSSION

In the past, the main role of MRI in patients with hearing loss was the detection of acoustic neuromas, and imaging of the labyrinth has received little attention.

The bony labyrinth is well-imaged with high-resolution computed tomography. The membranous labyrinth with its surrounding perilymph is well seen as an intermediate-signal-intensity structure against the low-signal intensity of the temporal bone on T1-weighted MRI. The fluid in the cochlea and vestibule produces a high signal intensity on T2-weighted images.

Gadolinium enhancement on T1-weighted sequences is well documented in a number of inflammatory as well as neoplastic lesions, reflecting the breakdown in the blood-brain barrier and leakage of the agent into the lesion.^{4,5} We believe the labyrinthine enhancement we see in the cases reported represents accumulation of gadolinium in the labyrinth following leakage through the abnormal labyrinthine membrane.

Thus, gadolinium enhancement of the labyrinth appears to be a highly specific sign of labyrinthine disease. The sensitivity of this finding remains to be determined. This study was not designed to evaluate

the incidence of labyrinthine enhancement in patients with hearing loss and vertigo. The yield of the MRI will depend on how careful the clinical screening of the patients was. Many of the studies in our institution show normal findings.

We have recently reported on five patients with enhancement of the cochlea and vestibule correlating with both subjective and objective alterations of the cochlea and vestibular function.³ Our current study also includes seven additional patients. The study confirms the validity of our initial observation correlating labyrinthine enhancement with severe loss of cochlear and/or vestibular function. Indeed, in all patients the enhancement of the cochlea correlates with a marked decrease in both objective and subjective cochlear function. The vestibular enhancement correlates with markedly abnormal objective and subjective vestibular function. The lack of vestibular enhancement correlates with the lack of symptoms. However, patients who are symptomatic but who have only mildly abnormal ENG findings may also not show enhancement. A similar threshold phenomenon was described in experimental studies of bacterial meningitis in dogs; areas of meningeal enhancement correlated with areas of pathologically proven meningeal inflammation, but there were several areas of milder inflammation that did not enhance with gadolinium.⁴

Enhancement limited to certain segments of the cochlea is a previously unreported finding. In two of our patients the location of enhancement correlated with the loss of hearing in the expected frequency mapped by the respective area of the cochlea. However, in two patients with segmental enhancement of the basal turn of the cochlea there was complete hearing loss.

The cause of the enhancement of the labyrinth in our series could be determined in a few patients but remained elusive in others.

Viral labyrinthitis is postulated as the most likely pathologic process in nine patients. Previous researchers have pointed out that the labyrinth may become involved in the course of specific viral infections such as measles, mumps (as seen in one of our patients), and upper respiratory tract infections and that sudden deafness may be caused by viral infection without clinical evidence of systemic involvement.⁶⁻⁹ Schuknecht and Donovan¹⁰ had examined the temporal bone pathologic findings in 12 ears with idiopathic sudden sensorineural hearing loss and found the histologic lesions were similar to those reported in known cases of viral cochleitis. The microscopic studies showed atrophy of the organs of Corti, tectorial membranes, and striae vasculares in different combi-

nations and of different severities.¹⁰ Viral labyrinthitis is the likely cause for enhancement in the two patients who had documented improvement in hearing over a period of several months correlating with resolution of the enhancement on MRI, as well as the patient in whom there was a documented elevation and subsequent fall of the rubella titers, and in the child who developed hearing loss following mumps orchitis. In six other cases, there was a concurrent or recent history of a viral illness.

Luetic labyrinthitis is also recognized as a cause of hearing loss and vertigo.⁷ In one of our patients with bilateral hearing loss from luetic labyrinthitis, only the most symptomatic ear enhanced, illustrating the threshold effect mentioned above.

Bacterial labyrinthitis usually follows a middle ear infection and results in sudden complete irreversible sensorineural hearing loss. The patient included in our series represents, to our knowledge, the first reported case of bacterial labyrinthitis imaged on gadolinium-enhanced MRI. It is worth mentioning that at the time of the imaging the infection in the middle ear was relatively mild and seemed to be responding to antibiotic treatment. However, enhancement of the cochlea is not specific for inflammatory lesions. A case report of cochlear enhance-

ment in a patient with a surgically proven intracochlear neuroma was recently reported,¹¹ and we have also encountered three such cases. Previously, intralabyrinthine neurinomas were rarely suspected on the basis of radiographic studies and rarely diagnosed during life, but they have been reported in histopathologic studies of temporal bones.¹² Since intracochlear neuromas are so rare, we do not know if they would present as sudden hearing loss. Thus, intralabyrinthine neuromas cannot be completely excluded unless resolution of labyrinthine enhancement can be documented over time.

In conclusion, gadolinium-enhanced MRI can, in some patients with acute hearing loss and/or vertigo, detect inflammatory lesions of the membranous labyrinth. Enhancement correlates with severely abnormal cochlear and/or vestibular function. Enhancement of certain segments of the cochlea correlates in some patients with the loss of the frequency mapped by the enhancing segment. Since the abnormalities seen on ENG and audiograms are nonspecific and only indicate a sensorineural problem, gadolinium-enhanced MRI may separate patients with retrocochlear lesions, such as acoustic neuromas, from patients in whom the abnormal process is labyrinthine or in the brain stem.

ACKNOWLEDGMENT — We thank Nancy Carnes for her editorial assistance in the preparation of this paper.

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PEDIATRIC AIRWAY RECONSTRUCTION AT GREAT ORMOND STREET: A TEN-YEAR REVIEW

I. LARYNGOTRACHEOPLASTY AND LARYNGOTRACHEAL RECONSTRUCTION

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One hundred eight consecutive patients with pediatric laryngotracheal stenosis requiring airway reconstruction over a 10-year period were reviewed. One hundred forty-nine operations consisting of 75 laryngotracheoplasties and 74 laryngotracheal reconstructions with costal cartilage grafting were performed. The Cotton grading scheme of preoperative stenosis was useful in predicting likelihood of decannulation. In all, 90 patients (83%) were decannulated.

KEY WORDS — cartilage, intubation, laryngotracheal stenosis, tracheostomy.

INTRODUCTION

Pediatric laryngotracheal stenosis is a difficult problem to manage. The patient requires a tracheostomy if the stenosis is severe, which in itself poses a significant risk of morbidity and mortality.¹ The goal of treating these patients is to restore the natural airway with a satisfactory voice.

Airway reconstruction is contemplated only for those patients who require a tracheostomy. Surgery for this condition has fallen into two types of procedures at our institution: laryngotracheoplasty²⁻⁴ and laryngotracheal reconstruction with costal cartilage grafting.⁴⁻⁶

Laryngotracheoplasty was first described by Evans and Todd² in 1974. This operation consists of ex-

panding the airway lumen via a castellated incision in the cricoid cartilage and upper tracheal rings (Fig 1).

Laryngotracheal reconstruction with costal cartilage grafting was developed primarily by Cotton.⁵ This operation involves a midline incision made anteriorly in the larynx and upper trachea. The posterior plate of the cricoid may also require division to increase the airway lumen sufficiently. A boat-shaped costal cartilage graft is used to expand the airway, and is placed anteriorly, posteriorly, or in both sites (Fig 2).

This article, the first of three, is devoted to describing our general experience in managing pediatric laryngotracheal stenosis. The second article will deal with those patients requiring more than one attempt

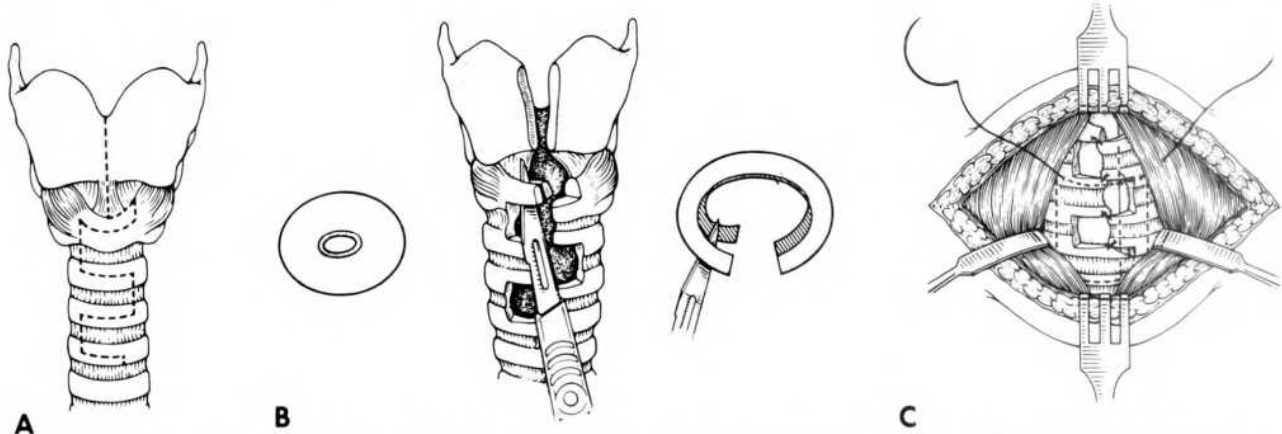


Fig 1. Laryngotracheoplasty. A) Castellated incision through cricoid cartilage and upper tracheal rings. B) Access to stenosis through castellated incision. Stenotic area may thus be excised. C) Airway is secured in expanded position with sutures.

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Presented at the International Workshop of Pediatric Laryngotracheal Stenosis, Leeds Castle, Kent, England, July 24-27, 1991.

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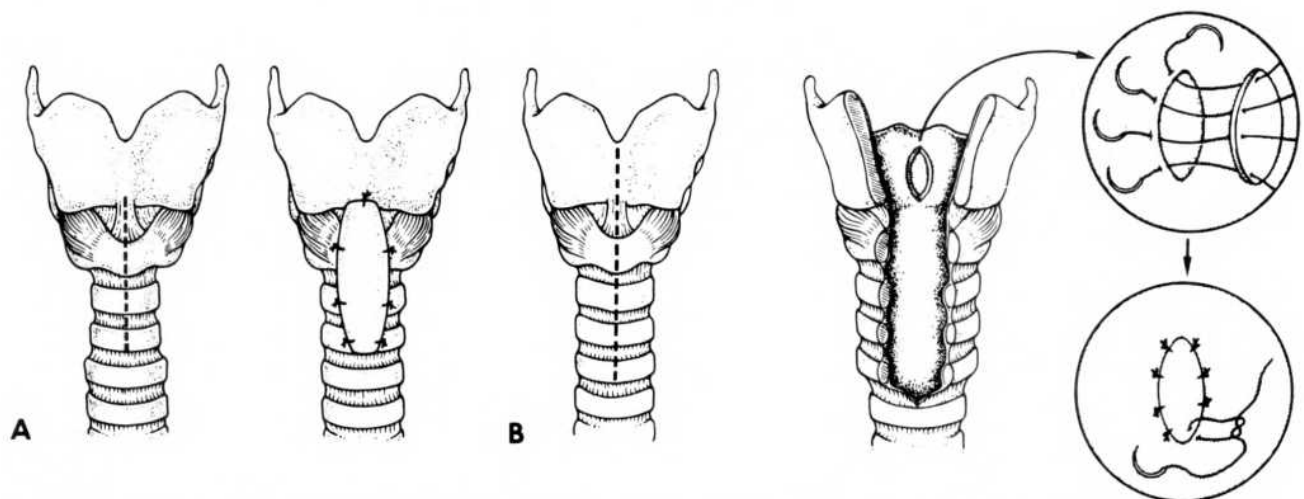


Fig 2. Laryngotracheal reconstruction. A) Anterior midline incision through airway. Costal cartilage graft is used to augment stenotic airway. B) Posterior plate of cricoid may also be divided to enhance airway lumen. Boat-shaped costal cartilage graft may be placed posteriorly as well as anteriorly.

at surgical reconstruction, and the last article is concerned with the goal of airway reconstruction: decannulation.

MATERIALS AND METHODS

A search was undertaken to identify all patients with pediatric laryngotracheal stenosis at The Hospital for Sick Children, Great Ormond Street, who required airway reconstruction from January 1, 1978, to January 1, 1988. These medical records were reviewed in January 1990, so that all patients studied would have a minimum of 2 years of postoperative follow-up. Patients were referred from throughout the United Kingdom and Europe, Scandinavia, the Middle East, Africa, and Cuba.

The degree of preoperative stenosis was assigned to one of four groups as described by Cotton et al.⁷ Grade 1 obstruction had less than 70% of obstruction of the lumen; grade 2 obstruction had between 70%

and 90% of the lumen obstructed. Grade 3 cases exhibited greater than 90% obstruction, but still had an identifiable lumen. Grade 4 stenosis existed when no lumen or fistula was present and no vocal cords were recognized; hence, grade 4 stenosis is a pouch with no epidermal connection.

RESULTS

One hundred eight patients who met the above criteria were found. All patients underwent tracheostomy, ranging in age from the day of birth to over 11 years old. Two thirds (73 patients or 68%) of the patients had their tracheostomy in the first 2 years of life. The early tracheostomies were primarily for intubation injuries, whereas the later tracheostomies were due to road traffic accident injuries (Fig 3).

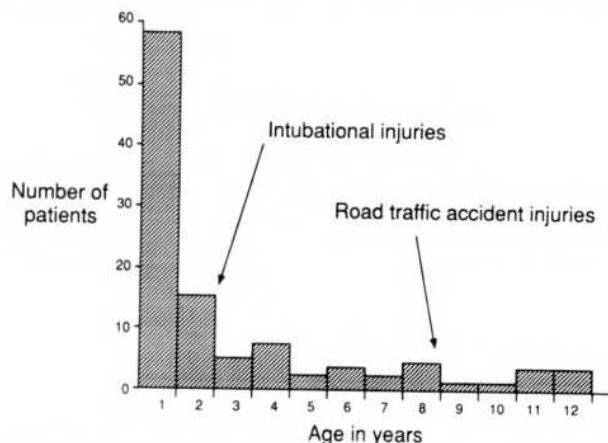


Fig 3. Age at tracheostomy. Earlier tracheostomies were primarily for intubation injuries, whereas later tracheostomies were due to road traffic accident injuries.

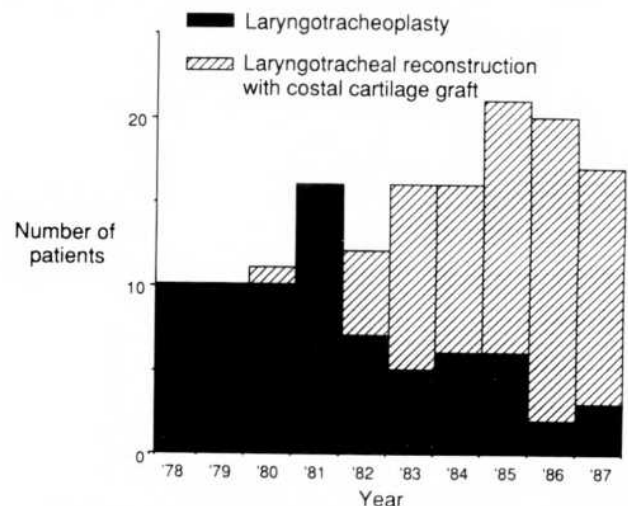


Fig 4. Airway reconstruction by year. Total of 149 airway reconstructions were performed over 10 years. General increase in surgical case load was observed, from 10 to 17 operations annually.

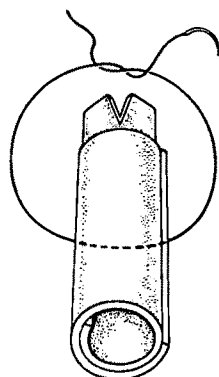


Fig 5. Silastic "Swiss roll." Stent used to keep airway lumen open for both laryngotracheoplasties and laryngotracheal reconstructions.

A total of 149 primary and revisional airway reconstructions on the 108 patients were performed over the 10-year period, consisting of 75 laryngotracheoplasties and 74 laryngotracheal reconstructions (Fig 4). Age at primary reconstruction varied from 6 months to 16 years, but most often the operation took place in the second or third year. Sixty-eight patients had laryngotracheoplasty as the primary procedure; 40 had laryngotracheal reconstruction. In the laryngotracheal reconstruction category, 19 patients had anterior costal cartilage grafting, 7 had posterior grafts, and 14 underwent both anterior and posterior grafting.

Laryngotracheoplasty was the operation of choice in the early portion of this study. The first laryngotracheal reconstruction with costal cartilage grafting was done in September 1980, and its use increased so much that by the end of the study period it had almost entirely replaced laryngotracheoplasty. There was a general increase in the surgical case load over the years as well.

The Silastic "Swiss roll" was used to stent the airway lumen open during the healing phase postoperatively for both laryngotracheoplasties and laryngotracheal reconstructions (Fig 5). The Silastic roll was removed usually at the sixth week after operation.

In all, 90 patients (83%) were decannulated during the study period. The Cotton staging scheme confirmed decreasing likelihood of decannulation with increasing grade of stenosis. Eighty-eight percent of the patients with grade 1 stenosis were decannulated; the percentage decreased to 50% of those with grade 4 (Fig 6).

Nine patients suffered neck wound infections, which all healed without incident. No chest wound infections were encountered. Four patients required a chest drain for violation of the pleura during costal

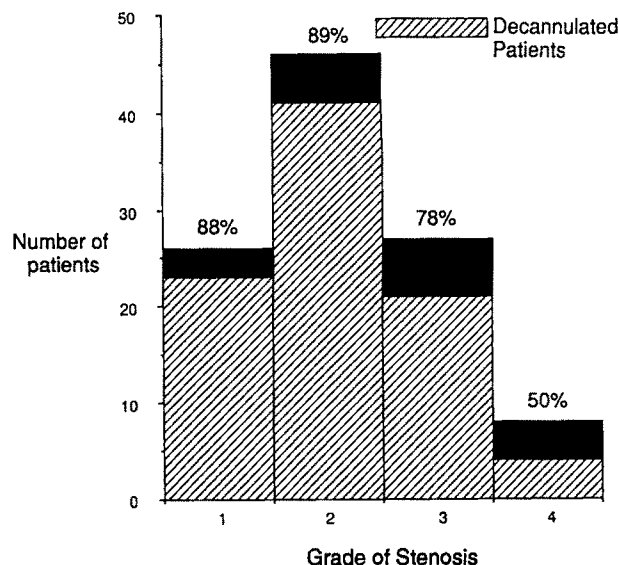


Fig 6. Decannulation rates after airway reconstruction by grade. Eighty-eight percent of patients with grade 1 were decannulated, and 50% of those with grade 4.

cartilage harvesting. Four patients had dislodgment of the Silastic stent, despite a transfixion suture to prevent this occurrence. Three of the four were found to have the stent in the lower trachea, all without respiratory distress. These stents were removed without incident by bronchoscopy. The remaining patient expelled the Silastic roll during a severe coughing fit. Three patients suffered respiratory arrest from obstruction of the tracheostomy tube; one had complete recovery, but two others died. One patient died several hours postoperatively of an unrecognized pneumothorax, and another patient died at home in unclear circumstances.

DISCUSSION

Treatment of laryngotracheal stenosis must be individualized to the patient's needs, but follows a definite pattern. Most patients are born prematurely and require intubation for bronchopulmonary dysplasia.⁸ Many require multiple reintubations because of tube dislodgment or for operations unrelated to the airway, and these inevitably cause airway trauma. The patient fails multiple attempts at extubation and undergoes a tracheostomy.

At follow-up microscopic laryngoscopy and bronchoscopy, stenosis of the airway is diagnosed. The stenosis is assessed and documented, and the carbon dioxide laser may be used to increase the airway lumen diameter by vaporizing granulation tissue and webs. The endoscopy is repeated in a few months to allow for laryngeal growth. If the patient is still not able to be decannulated, then airway reconstruction is considered.

As a rule, reconstruction is delayed until the patient reaches 2 years of age or 10 kg in weight. Experience has shown that patients much smaller or younger pose technical surgical difficulties due to their small size. Most cases can be managed with laryngotracheal reconstruction using an anterior costal cartilage graft. Posterior grafting is indicated primarily when interarytenoid scarring tethers the mobility of the vocal cords. Anterior and posterior grafting is used when the stenosis is severe, so that maximal airway augmentation can be achieved.

The Silastic stent is left in place normally for 6 weeks. The patient then has the stent removed endoscopically with release of the transfixion suture. Ten days later, microscopic laryngoscopy and bronchoscopy is done. If excessive granulation tissue is encountered, the laser is used to decrease the chance of restenosis. The patient undergoes microscopic laryngoscopy and bronchoscopies regularly until either judged fit for decannulation or considered for revisional reconstruction; this is a clinical judgment based on progress achieved over time.

The evolution of the management of pediatric laryngotracheal stenosis is apparent from this retrospective analysis. The laryngotracheoplasty is an elegant operation designed for congenital subglottic stenosis, but is technically difficult when the stenosis is severe enough to obliterate surgical landmarks for the castellated incision. This is often the case when the stenosis is due to perichondritis and consequent fibrosis. Augmenting the stenosed airway segment with a costal cartilage graft is a straightforward way of increasing the airway lumen, and so is now favored by many surgeons.

The type of stent and even the issue of whether a

stent is necessary are still controversial.^{9,10} Each center has its own preferences and tends to use one particular type of stent. The Silastic Swiss roll exerts gentle pressure on the inner wall of the airway, is easily fitted to the needs of the individual patient, and in most cases allows some degree of voice production. Silastic has been criticized by others as inducing granulation tissue formation,⁶ but we have not found it to be an overwhelming problem.

A uniform staging scheme is important if progress is to be made in managing pediatric laryngotracheal stenosis. At the time of writing, no universally agreed on system exists. Cotton has proposed a staging plan that we have found to be useful and easy to apply to retrospective studies. Our results show increasing difficulty of achieving decannulation with increasing severity of stenosis, which one would expect if the staging plan is to be useful. In addition, the staging system is simple enough so that it can be applied retrospectively to almost every patient, even if documentation is scanty.

The four deaths in our series illustrate the difficulties in managing patients with the complex problem of laryngotracheal stenosis. However, a 4% mortality rate is not out of line for managing pediatric tracheostomies.¹ Violation of the pleura during costal cartilage harvesting is managed by chest tube drainage and does not pose a problem providing it is diagnosed with an immediate postoperative chest radiograph.

Pediatric laryngotracheal stenosis is a difficult disease to manage, but can be treated successfully in most patients. Another article will focus on patients who require more than one attempt at airway reconstruction to achieve decannulation.

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SPONTANEOUS REGRESSION OF JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

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There is debate concerning the natural history of juvenile nasopharyngeal angiofibromas, especially whether or not they can spontaneously regress. Often claimed, spontaneous regression has not been well documented. To our knowledge, this is the first report in which a biopsy-proven juvenile nasopharyngeal angiofibroma spontaneously resolved. A second, less well-documented case is discussed.

KEY WORDS — nasopharyngeal neoplasms, sclerosing angioma.

Juvenile nasopharyngeal angiofibroma (JNA) is a benign tumor typically affecting adolescent boys. Generally, JNAs are believed to behave in a locally invasive manner and to locally recur in up to 25% of cases.^{1,2} The characteristic geographic pattern of growth has been well outlined by Neel et al.³ Despite these descriptions of this tumor's usual pattern of behavior, there is nonetheless debate concerning the natural history of this tumor in terms of its ability to malignantly degenerate,^{2,4-12} present with distant metastasis,^{13,14} and, as discussed here, spontaneously resolve. We present a patient with a biopsy-proven recurrent JNA who demonstrates no evidence of tumor on clinical examination or computed tomography (CT) scan 15 years later.

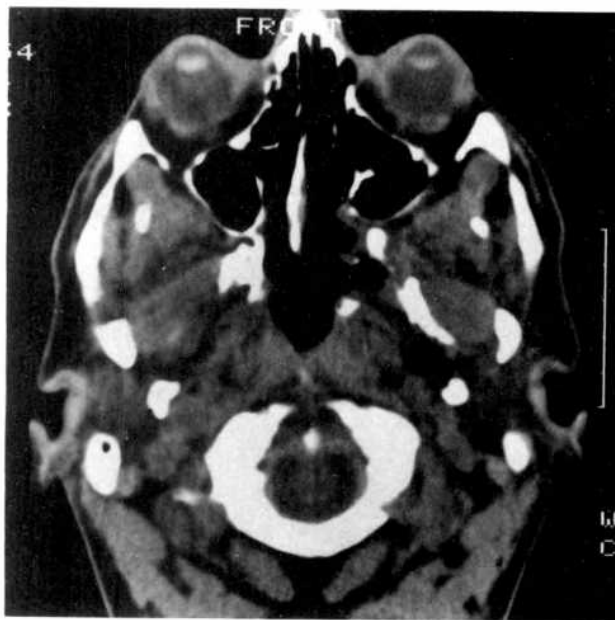
CASE REPORT

A 13-year-old boy presented in September 1969 with a several-year history of severe bilateral nasal obstruction and recurrent epistaxis. He underwent surgical resection of his JNA via a transpalatal approach. He presented again in May 1971 with epistaxis and on physical examination was noted to have a recurrence in the nasopharynx. This was initially treated with chemical cautery, but because of persisting epistaxis as well as a persisting nasopharyngeal mass, surgical resection was again performed, this time via a transnasal approach. He presented again in December 1972 with recurrence of epistaxis and a left-sided nasopharyngeal mass. He was placed on a regimen of 2.5 mg of Premarin per day, which seemed to reduce the frequency of his nosebleeds. The nasopharyngeal mass, however, continued to grow. At this point, the patient was referred to the University of Minnesota Hospital and Clinic. In April 1973 the patient underwent a third resection of the tumor via an intraoral tripartite approach¹⁵ accompanied by ligation of the left external carotid artery. The tumor

involved the left side of the nasopharynx with extension to the posterior inferior turbinate and the posterior nasal septum, through the pterygomaxillary fissure into the pharyngomaxillary space, and through the anterior wall of the sphenoid sinus. Pathologic analysis of the tissue demonstrated recurrent JNA. Postoperatively, the patient did well until May 1975, when he experienced progressively worsening left nasal obstruction. Physical examination revealed a mass broadly attached to the left superior and lateral nasopharyngeal walls. Biopsy of this mass revealed recurrent JNA. The patient was not significantly bothered by his unilateral nasal obstruction and was therefore managed expectantly. In May 1979, he continued to complain of left-sided nasal obstruction, and physical examination revealed a significant septal deviation obstructing the left side of the nose along with persistence of the nasopharyngeal mass, unchanged in appearance since 1975. He underwent septoplasty and a repeat biopsy that again revealed recurrent JNA. He was subsequently lost to follow-up but returned to the clinic in November 1990 for an unrelated otolaryngologic problem. Examination of his nasopharynx at that time revealed no evidence of tumor and he denied any complaints of nasal obstruction or epistaxis. Nasopharyngeal imaging via high-resolution CT scanning with contrast in April 1991 provided radiographic confirmation of tumor resolution (see Figure).

DISCUSSION

The natural history of JNA is not completely understood. Although this tumor has been said to regress and spontaneously involute at or about the age of puberty, there is little authenticated documentation that untreated lesions do so. Ringertz¹⁶ in 1938 stated that spontaneous regression of these tumors usually occurs when the patient reaches the age of 20



Enhanced computed tomogram from 1991 demonstrating no tumor in nasopharynx at level of 1975 recurrence. Diverticulum on left lateral nasopharyngeal wall and absence of left pterygoid plates are result of 1973 resection.

to 25 by both resorption and disintegration with breaking off of the peripheral processes of the tumor, although he offered no support for his contention. In 1948, Martin et al¹⁷ stated that it is probable that some cases of nasopharyngeal fibroma of moderate size occur and regress spontaneously. They supported their statement with the case of a 15-year-old boy who was completely asymptomatic and on physical examination was incidentally noted to have a nasopharyngeal mass. Over 2½ years the tumor was not noted to regress, and there was never tissue confirmation of the diagnosis. Dane¹⁸ in 1954 reported a JNA in the process of regression. The spontaneous regression in this case, however, was assumed, with the only documentation of the regression being the patient's history. Witt et al¹¹ described a case that they termed a spontaneous regression over 16 months, but

the patient had been treated with two surgical procedures and two courses of radiotherapy. It has been well documented that radiotherapy can continue to affect JNAs for up to several years.¹⁹ Stansbie and Phelps²⁰ reported in 1986 the involution of residual JNA documented by means of serial CT scans over a 3-year period. There was no tissue confirmation of the suspected recurrence. It has been our experience that occasional recurrent JNAs are often difficult to distinguish from fibrosis on CT scan. Further, Bremer et al²¹ reported two instances in which they reexplored patients on the basis of a tumor blush noted on angiography and in both cases found no gross tumor at the time of exploration. These experiences call into question the reliability of radiographic imaging in diagnosing recurrent JNA. Finally, Jacobsson et al²² described the regression of a JNA that recurred following surgical resection. The recurrent tumor was treated with embolization of all branches of the external carotid artery, and over 6 years it was followed up with serial CT scans and noted to regress.

Because of the questionable documentation in the literature for spontaneous regression of JNAs, some authors have denied that it can occur at all.^{2,23} We believe that the case described in this paper provides evidence that JNAs can spontaneously regress. Further, we have a second case of a 13-year-old boy who, after a surgical resection of his initial tumor, developed a recurrence that was followed clinically and noted to progressively decrease in size. Correspondence with his mother in 1973 and with the patient in 1990 revealed that he was having no clinical difficulty and was seeking no further medical treatment for this problem. We present this case as an aside because of lack of objective documentation of spontaneous resolution. These cases lead us to conclude that JNAs, in at least a minority of instances, can spontaneously resolve. To our knowledge, ours represents the only documented biopsy-proven case of JNA with spontaneous resolution.

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ADDENDUM

Subsequent to the writing and submission of this article, L. S. Weprin and P. T. Siemers reported a case wherein a JNA spontaneously regressed over a 12-year period without any treatment (Spontaneous Regression of Juvenile Nasopharyngeal Angiofibroma, *Arch Otolaryngol Head Neck Surg* 1991;117:796-9). The JNA had been diagnosed by biopsy in a child 11 years of age. We believe that this case offers further support that JNA, in a minority of cases, can spontaneously involute.



7TH WORLD CONGRESS FOR BRONCHOLOGY & BRONCHESOPHAGOLOGY

The 7th World Congresses for Bronchology & Bronchoesophagology will be held Sept 28-Oct 2, 1992, at the Mayo Clinic and Mayo Medical Center in Rochester, Minnesota. For further information, contact Udaya B. S. Prakash, MD, Secretary-General & Director, 7th WCB & WCBE, East-18, Mayo Clinic, Rochester, MN 55905.



THE DEAFNESS RESEARCH FOUNDATION 1993 RESEARCH GRANTS AVAILABLE

The Deafness Research Foundation invites applications for 1993 grant support of research projects directed to any aspect of the ear, eg, investigation of function, physiology, biochemistry, genetics, anatomy, or pathology. Grant support is given for one year, in an amount that cannot exceed \$15,000, but can competitively be renewed for one or two additional years. Applications are reviewed for the scientific merit of the proposed investigations and for their direct or potential clinical value. The deadlines for applications for 1993 grant support are as follows: first year applications should be postmarked by July 15, 1992, and renewal applications should be postmarked by August 15, 1992. For information and applications, contact Wesley H. Bradley, MD, Medical Director, The Deafness Research Foundation, 9 East 38th Street, New York, NY 10016; telephone (212) 684-6556; fax (212) 779-2125.

OTOLARYNGOLOGIC MANIFESTATIONS OF THE MUCOPOLYSACCHARIDOSES

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A retrospective review of 45 children with mucopolysaccharidoses was performed to determine the frequency of complications related to the head and neck. In this series, every patient had at least one complication involving the head and neck region, and in over half, operative intervention by the otolaryngologist was required. Upper airway obstruction occurred in 17 (38%) and necessitated a tracheostomy in 7 (16%). Cervical spine instability occurred in 8 (18%), making airway management difficult. Recurrent respiratory infections occurred in 17 (38%), and chronic recurrent middle ear effusions were noted in 33 (73%). This review demonstrates that children afflicted with the mucopolysaccharidoses frequently have otolaryngologic-related complications that are common throughout their life span and often the primary management issue in their continuing care. The otolaryngologic management of these patients is outlined based on the results of this study and review of the relevant literature.

KEY WORDS — lysosomal storage diseases, metabolic storage diseases, mucopolysaccharidoses, upper airway obstruction.

INTRODUCTION

The mucopolysaccharidoses (MPSs) are six closely related, genetically determined lysosomal storage diseases. They are each characterized by a specific enzymatic defect that results in an accumulation of incompletely degraded mucopolysaccharides within the lysosome. Depending on the particular mucopolysaccharide by-product and the affected tissue, a wide range of clinical manifestations can occur (Table 1^{1,2}). They are all inherited in an autosomal recessive pattern, except for Hunter's syndrome, which is X-linked. They occur in all ethnic groups, and in general have a combined incidence of 1 in 30,000 to 150,000 live births.³ Confirmation of the clinical diagnosis is by specific enzyme assay,² and amniocentesis may allow prenatal diagnosis.⁴ They are all clinically progressive, but vary in the degree and rate of specific organ deterioration. Although there is no definitive treatment for the MPSs,¹ enzyme replacement by bone marrow transplantation has been attempted with some encouraging results.⁵⁻⁷

The prototype MPS is Hurler's syndrome (MPS I H). Patients appear normal at birth, but later are found to have retarded intelligence and short stature. Characteristic findings include a large head, flat nose, upturned nostrils, coarse facial features, hirsutism, corneal clouding, macroglossia, prominent forehead, joint stiffness, skeletal deformities (dysostosis multiplex), recurrent respiratory infections, otitis media,

upper airway obstruction, persistent rhinorrhea, and obstructive hydrocephalus. The diagnosis is usually established by 6 to 24 months, and death ensues by age 10 years. Deficiency of the same enzyme, α -L-iduronidase, also causes Scheie's syndrome (MPS I S) and the phenotypically intermediate Hurler-Scheie compound type (MPS I H/S). Patients with Scheie's syndrome are much less severely affected than those with MPS I H and are recognized later and live longer. Patients with the compound syndrome have symptoms and complications that are intermediate between types I H and I S.^{2,3}

Hunter's syndrome (MPS II) is clinically distinguished from MPS I by the lack of corneal clouding, a longer life expectancy, less severe mental retardation, and an X-linked pattern of inheritance. Type II A is more severe in its manifestations and is clinically detectable by age 2 to 4 years, with death occurring in the second decade. Type II B is milder and is recognized later in childhood, with life expectancy into the fifth and sixth decades.^{2,3}

Patients with Sanfilippo's syndrome (MPS III) have an enzyme deficiency involving the breakdown of heparin sulfate. Clinically, the four subtypes of Sanfilippo's syndrome (A-D) are indistinguishable, but they differ biochemically in the specific enzyme deficiency. These patients have severe central nervous system involvement but only mild somatic

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Presented at the meeting of the American Society of Pediatric Otolaryngology, San Diego, California, May 19, 1989.

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TABLE 1. CLASSIFICATIONS OF MUCOPOLYSACCHARIDOSIS

Class*	Eponym	Enzyme Deficiency	Characteristics
I H	Hurler's	α -L-Iduronidase	Mental retardation, corneal clouding, coarse features
I S	Scheie's	α -L-Iduronidase	Normal intelligence and near-normal stature
I H/S	Compound	α -L-Iduronidase	Intermediate phenotype
II	Hunter's	Iduronate-2-sulfatase	Intermediate intelligence, no corneal clouding
III A	Sanfilippo's A	Heparan <i>N</i> -sulfatase	Mild somatic changes, severe mental retardation
III B	Sanfilippo's B	α - <i>N</i> -acetylglucosaminidase	Same as III A
III C	Sanfilippo's C	α -Glucosaminidase- <i>N</i> -acetyltransferase	Same as III A
III D	Sanfilippo's D	<i>N</i> -acetyl-glucosamine-6-sulfatase	Same as III A
IV A	Morquio A	Galactosamine-6-sulfatase	Instability of first and second cervical vertebrae, skeletal dysplasia, normal intelligence
IV B	Morquio B	β -Galactosidase	Same as IV A but less severe
V	Renamed as Scheie's†		
VI	Maroteaux-Lamy	<i>N</i> -acetylgalactosamine-4-sulfatase	Normal intelligence, phenotype like that of I H
VII	Sly	β -Glucuronidase	May have phenotype like that of I H

*McKusick et al¹ originally proposed numeric classification of types I to V, and this has subsequently been extended.

†Reclassified as type I S when enzyme defect was shown to be same as that in Hurler's syndrome. Thought to represent allelic mutation at same gene locus.²

features of MPS. Onset of symptoms occurs between 3 and 6 years of age, and death ensues by the second or third decade. Despite being the most frequent type of MPS, it is perhaps the most underdiagnosed, since the lack of overt somatic features allows it to be mistaken for a nonspecific form of mental retardation.³

The predominant clinical features found in Morquio syndrome (MPS IV) are those related to the skeletal system and its secondary effects on the spinal cord. Patients are dwarfed, with normal intelligence, and have facial features similar to those with Hurler's syndrome. Its hallmark is severe skeletal dysplasia (spondyloepiphyseal dysplasia), joint hypermobility, and absence or severe hypoplasia of the odontoid process of the axis. Acute or chronic cervical myelopathy is common.^{2,3}

Maroteaux-Lamy syndrome (MPS VI) is clinically similar to Hurler's syndrome, except that intelligence is preserved and there is a longer life expectancy. The diagnosis is usually established by 2 to 3 years.^{2,3}

Sly syndrome (MPS VII) is very rare, with fewer than 20 cases described in the literature.² The clinical manifestations have been described as being similar to those found in Hurler's syndrome, although reported cases have shown a variable phenotype.^{2,3}

Sporadic reports in the anesthesia literature have described the difficulties of intubation and acute perioperative management of patients with types of MPS.⁸⁻¹¹ Chronic sinusitis, otitis media, upper air-

way obstruction,¹² sleep apnea,^{13,14} cervical instability,^{15,16} frequent dental problems,¹⁷ odontogenic cysts,^{2,18} and recurrent respiratory infections have been noted in case reports and in small series focusing on specific MPS types. The following retrospective study of 45 patients with MPS is unique, because it is the largest series to be reported in the surgical literature and contains representative patients from all MPS types. The purpose of this report is to demonstrate the high incidence of head and neck manifestations within this entire group of complex, related metabolic disorders, compare the otolaryngologic manifestations between MPS types, and provide the head and neck surgeon with specific management guidelines for dealing with these unfortunate children.

MATERIALS AND METHODS

The patients included in this study received diagnoses and were treated at the University of California Center for the Health Sciences, Los Angeles; Children's Hospital of Los Angeles; or the University of California, Irvine, Medical Center. All patients had the diagnosis established by the presence of the characteristic clinical and laboratory findings consistent with a specific MPS subtype (Table 1).

Patients were identified from the respective hospital records by a computerized data search for patients with a discharge diagnosis of MPS during the years 1979 to 1989. An additional four patients were identified from the records of the genetics laboratory at

TABLE 2. INCIDENCE OF OTOLARYNGOLOGIC COMPLICATIONS AND MOST COMMONLY PERFORMED HEAD AND NECK SURGICAL PROCEDURES IN MUCOPOLYSACCHARIDOSES AS FUNCTION OF CLINICAL TYPE

	Type						Total	
	I	II	III	IV	VI	VII	No.	%
Total patients	13	7	12	6	5	2	45	
Middle ear effusion	10	3	12	4	3	1	33	73%
Middle ear pressure equalization tubes	6	3	1	2	3	1	16	36%
Airway obstruction	7	1	1	4	3	1	17	38%
Tonsillectomy and adenoidectomy	5	1	2	1	3	1	13	29%
Tracheostomy	3	0	0	0	3	1	7	16%
Rhinosinusitis	5	4	2	1	4	1	17	38%
Instability of first and second cervical vertebrae	0	0	0	5	1	2	8	18%

Children's Hospital of Los Angeles, where all the enzyme assays are done for the greater Los Angeles area.

Included in this study were 13 patients with type I H, 7 patients with type II, 12 patients with type III, 6 patients with type IV, 5 patients with type VI, and 2 patients with type VII. Seven patients had died by the time of the review. The patients' clinical records were reviewed, and the appropriate radiographs and histologic studies examined.

RESULTS

Table 2 shows the most common head and neck complications found in the different MPS types. At least one complication related to the head and neck region occurred in every case of MPS reviewed, and it usually necessitated otolaryngologic consultation. Surgical therapy by the otolaryngologist was required in 23 patients (51%) and often required multiple procedures and anesthetics. The most common operative procedures performed by the head and neck surgeon were insertion of middle ear ventilation tubes (36%), tonsillectomy and adenoidectomy (29%), and tracheostomy (16%).

Clinically significant upper airway obstruction

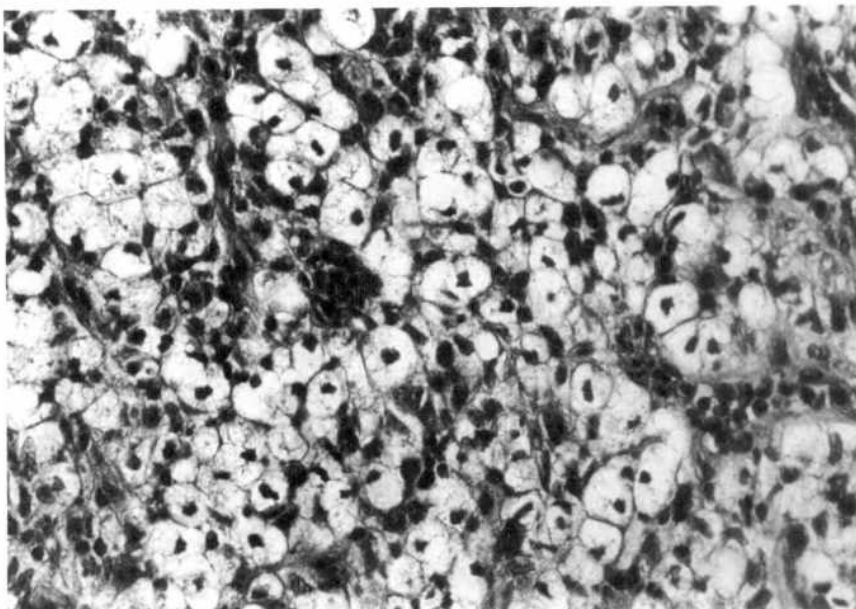
occurred in 17 patients (38%), and ultimately 7 of these patients (16% of all patients or 41% of those with airway obstruction) had cor pulmonale and required a tracheostomy for relief. Although upper airway obstruction occurred in all types, patients with types I, IV, VI, and VII were more likely to have obstructive problems and require a tracheostomy. All patients with upper airway obstruction were initially treated with adenotonsillectomy. Adenotonsillectomy offered a variable time of relief from airway obstruction that ranged from 1 month to 5 years. Ultimately, 44% of patients who had an adenotonsillectomy for obstruction failed and went on to have a tracheostomy.

Seven patients had cervical vertebral instability documented on radiographs, and the most common finding was a nontraumatic atlantoaxial subluxation. Cervical instability occurred in MPS types IV, VI, and VII. Progressive quadriplegia occurred in three of five patients with MPS type IV. Two patients (one type VI and one type VII) with cervical instability and concurrent airway obstruction underwent a tracheostomy. No neurologic sequelae occurred as a result of any surgical procedure.

Rhinosinusitis as defined by radiographic evidence of sinus opacification and/or persistent rhinorrhea occurred in 17 patients (38%). Rhinosinusitis and persistent rhinorrhea were unresponsive to conservative medical management and sinus irrigation in most, and adenotonsillectomy was only effective in 25%.

Otologic complications were frequent in all MPS types. Chronic and recurrent otitis media occurred in 33 patients (73%). Indications for middle ear ventilation were 1) a persistent effusion for more than 12 weeks despite antibiotics or 2) recurrent otitis media while on antibiotic suppression. At least one set of middle ear ventilation tubes was placed in 16 patients (48% of those patients with chronic otitis media). Middle ear effusion was most common in MPS III, but rarely necessitated middle ear ventilation (only 1 of 12 patients). However, if all type III patients with middle ear effusion are excluded, over 75% of patients with middle ear effusion required tubes. One third of the patients had more than one episode of persistent otorrhea after myringotomy and insertion of middle ear tubes. All cases but one resolved with antibiotics and dry ear precautions. One patient required a simple mastoidectomy to control persistent otorrhea, and was found at operation to have extensive granulation tissue filling the middle ear and mastoid cavity. Histologic analysis of this tissue demonstrated foamy histiocytes with intracellular mucopolysaccharide deposits, which are typical of the cellular changes found in MPS (Fig 1). Sensori-

Fig 1. Mucopolysaccharide deposition in cells of middle ear biopsy specimen of patient with mucopolysaccharidosis type VI (H&E, original x100). Note characteristic foamy macrophages engorged with intracellular mucopolysaccharide.



neural hearing loss (as defined as a boneline of greater than 30 dB in three or more frequencies) was seen in 4 patients, and occurred alone without a history of chronic otitis media in only 1 patient. All patients with sensorineural hearing loss used at least one hearing aid.

CASE REPORTS

The following patients are presented to illustrate



Fig 2. (Patient 1) Typical gargoylic facies of patient with mucopolysaccharidosis type VI. Note characteristic coarse facial features, flattening of nasal bridge, large head, patulous lips, protruding tongue, and short neck obscuring tracheostomy tube (arrow).

the problems associated with the management and treatment of patients afflicted with the MPSs.

Patient 1. A 16-year-old boy with MPS was considered normal by his parents until his second year of life. At this time his facial features began to become coarse, and the diagnosis of Maroteaux-Lamy syndrome was established by enzyme assay. The patient had a long history of chronic nasal congestion and repeated bouts of otologic and pulmonary infections. The patient also had reactive airway disease. His appearance was typical of patients with the MPSs (Fig 2).

At age 12, because of airway obstruction and chronic rhinosinusitis, the patient underwent a tonsillectomy, an adenoidectomy, and limited palatopharyngoplasty. At the time of operation, his large tongue and short neck precluded orotracheal intubation and necessitated blind nasotracheal intubation. Two years later, the patient developed increasing upper airway distress, sleep apnea, and cor pulmonale. The patient was admitted to the hospital for an elective tracheostomy. The night before operation, he suffered a cardiopulmonary arrest, and an emergent bedside tracheostomy was done after multiple failed attempts at intubation. The larynx was found at the sternal notch, and a very soft and pliable trachea was located in a substernal position. At bronchoscopy he was found to have marked tracheal collapse, and the submucosa of the proximal tracheal wall was thickened. Biopsy of this area revealed intracellular mucopolysaccharide deposits. The patient later underwent a submental and cervical lipectomy and a 50% volume reduction of the base of tongue. He remains tracheostomy-dependent 3 years postoperatively.



Fig 3. (Patient 2) Sagittal magnetic resonance imaging scan of upper cervical spine, showing hypoplasia of odontoid process of axis (arrow).

Patient 2. An 8-year-old boy with MPS VII was considered normal by his parents until the age of 1 year. He had nearly constant nasal congestion and otitis media. At age 5 he underwent an adenotonsillectomy, limited palatopharyngoplasty, and intranasal polypectomy. Histologic analysis of the tissues removed revealed mucopolysaccharide infiltration. He had eight sets of middle ear ventilating tubes. At each successive administration of anesthetic, airway control was noted to be increasingly difficult. At the age of 7 he had progression of his upper airway obstruction, as evidenced by sleep difficulties and cor pulmonale. A sleep study showed significant nocturnal hemoglobin desaturation. In addition, cervical radiographs revealed abnormalities of the upper cervical vertebrae, and magnetic resonance imaging showed hypoplasia of the dens (Fig 3). He subsequently underwent an elective tracheostomy, at which time the surgeons were careful to limit cervical motion and flexion of his neck. A repeat sleep study done postoperatively showed resolution of his sleep apnea. He remains tracheostomy-dependent 2 years postoperatively.

DISCUSSION

The results of this series demonstrate that patients afflicted with the MPSs frequently have complications related to the head and neck region. Obstructive upper airway disease was one of the most common and life-threatening complications in this series. It

occurred in 17 (38%) patients and was found in all six types. It was most frequent in types I, IV, VI, and VII, and these patients were more likely to have sleep apnea or cor pulmonale and to require a tracheostomy. In this series, airway obstruction was uncommon in types II and III, in contrast to a reported high incidence of airway obstruction in type II patients.¹³

Airway obstruction in MPS patients is caused by a combination of a narrowed trachea, thickened vocal cords, adenotonsillar hypertrophy, macroglossia, a short neck, an abnormally shaped, overhanging epiglottis, and/or copious pulmonary and nasal secretions.^{12,13} The condyles are reduced in size, limiting mandibular excursion. Because of the high position of the larynx, patients may be obligate nasal breathers and have marked airway obstruction with nasal congestion.¹² Deformities of the thoracic cage lead to decreased chest wall compliance and a mixed obstructive-restrictive pattern of pulmonary disease. Reactive airway disease, which was common in this study, became increasingly difficult to control in the face of persistent rhinosinusitis, poor mucociliary clearance, and thickened pulmonary secretions. Involvement of the distal tracheobronchial tree by mucopolysaccharide deposits leads to a weakening of the tracheal cartilage, with subsequent collapse and narrowing of the airway.^{12,13}

The management of the obstructed airway begins with adenotonsillectomy. In many instances, adenotonsillectomy only resolved the problem temporarily, and invariably tracheostomy was necessary. Because of poor mucociliary clearance, patients commonly developed recurrent tracheitis and obstruction of the tracheostomy tube by thickened secretions. Frequent bronchoscopy was necessary to ensure a patent airway. In patient 1 of this series, redundant cervical soft tissue periodically obstructed the tracheostomy tube. Ultimately, a cervical and submental reduction lipectomy was helpful. Eventually, distal tracheal and bronchial involvement may necessitate continuous positive airway pressure.

Hearing problems were common in all six types of MPS, and were usually mixed. Poor middle ear ventilation is thought to occur because of chronic eustachian tube obstruction and thickened middle ear secretions.² Deformity of the ossicles has also been described in Hunter's syndrome.² The mechanism responsible for sensorineural hearing loss is unclear. One report of a temporal bone in a patient with Hunter's syndrome showed that the organ of Corti was normal, but that the cells of the spiral and vestibular ganglia were engorged with foamy storage material.¹⁹ Three sets of temporal bones from patients with Hurler's syndrome were reported to show

otitis media, residual mesenchyme in the round window niche, partial occlusion of the middle ear cavity, and basophilic concretions within the stria vascularis.²⁰

In the present series, 73% of patients had a history of chronic otitis media, and nearly half of these patients required placement of middle ear ventilation tubes. Children with MPS III were most commonly noted to have middle ear effusion, but were the least likely to require tubes. Middle ear postintubation otorrhea was common in all patients with tubes, but usually resolved with conservative therapy. Sensorineural hearing loss was documented in four patients, and in only one patient did hearing loss occur without a history of chronic otitis media. The lack of documentation of sensorineural hearing loss in this series and in the literature may be related to the difficulty of assessing hearing in children, especially those who are mentally retarded. The incidence of sensorineural hearing loss and temporal bone histopathology causing sensorineural hearing loss in patients with MPSs needs further investigation. Aggressive treatment of chronic otitis media and auditory rehabilitation will improve these patients' development and ability to communicate.

Abnormal head and neck radiographic findings are common in the MPSs. Absence or severe hypoplasia of the odontoid process of the axis and laxity of the vertebral ligaments occurs in MPSs I, IV, VI, and VII. Cervical myelopathy and spinal nerve root compression can also result from pachymeningitis cervicalis. Magnetic resonance imaging of the craniocervical region is helpful to determine the extent of involvement.²¹ Patients with MPSs will also have widening of the medial ends of the clavicle. The orbits are shallow, accounting for proptosis. The frontal sinus is hypoplastic, and the calvarium is thickened.¹⁷ The sella turcica is often enlarged, and the optic chiasm is elongated, creating the so-called J-shaped or omega sella. Hydrocephalus may be present and results from thickening of the meninges. Marked destruction of the sella turcica and cribriform plate, presumably caused by an arachnoid cyst, has been noted in a patient with Hurler's syndrome. It caused intermittent cerebral spinal fluid rhinorrhea.²

The surgical care of MPS patients proved to be difficult. Acute perioperative airway problems were common in this series and have been documented in case reports in the anesthesia literature.⁸⁻¹¹ Maintenance of the airway during induction of anesthesia was often difficult, and visualization was limited by the patient's narrowed upper airway. Temporomandibular joint arthritis and copious secretions frequent-

ly frustrated efforts to intubate. The use of antisialagogues often increased preexisting respiratory obstruction. Intubation often became increasingly difficult as the patient aged, and repeated inductions of anesthesia were associated with greater complications. Cervical instability occurred in types IV, VI, and VII, and has been also reported in type I.²¹ Although it was most common in type VI patients, who infrequently have airway obstruction, two patients in this series with vertebral instability and airway obstruction eventually required a tracheostomy. Even though none of the patients in this report experienced neurologic sequelae, it is recommended that either a neurosurgical or orthopedic assessment be obtained prior to any extension or hyperflexion of the neck. Although there were no operative deaths in this series, it is clear that general anesthesia in these children constitutes a major risk and should be approached with caution and only attempted when experienced anesthesiologists and otolaryngologists are readily available.

An unusual feature of this series is that it included two patients with the rare type Sly syndrome (MPS VII). The clinical manifestations of the fewer than 20 cases of Sly syndrome reported in the literature are similar to those found in Hurler's syndrome, although reported cases have shown a variable phenotype.^{2,3} The clinical characteristic of the 2 reported cases in this series were short stature, coarse facial features, no corneal clouding, and atlantoaxial instability. One patient had normal intelligence, and the other was retarded; one had chronic otitis media and obstructive airway disease that required a tracheostomy (patient 2).

The otolaryngologist-head and neck surgeon is an important member of the team of physicians providing care to children afflicted with MPSs. Airway obstruction should be suspected in all subtypes, and in types I, IV, VI, and VII it may be more severe. Atlantoaxial instability occurs in types I, IV, VI, and VII, and may place the cervical spine at risk during airway management. Poor mucociliary clearance often leads to chronic otitis media and rhinosinusitis. The surgical management of these unfortunate children is complex and challenging and demands a clear understanding of the clinical manifestations of this disease process. At times, interventions may only be supportive, as the disease process follows its ultimate course. However, with prompt recognition of complications and timely, appropriate intervention, these children and their families can enjoy a better quality of life and minimize or delay the handicapping effects of MPS.

ACKNOWLEDGMENTS — Dr Michel Philippart of the University of California, Los Angeles, School of Medicine and Department of Pediatrics provided invaluable assistance in identification of patients for review in this series. The authors thank Dr Jeffrey Birns for allowing us to include his patient in the report of cases.

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THIRD INTERNATIONAL CONFERENCE ON PEDIATRIC OTORHINOLARYNGOLOGY

The Third International Conference on Pediatric Otorhinolaryngology of the "European Pediatric Otolaryngology Working Group" will be held in Jerusalem, November 7-12, 1993. For more information, contact Prof Jacob Sadé, 14 Hagefen St, Ramat-Hasharon 47254, Israel; telephone 972-3-5494275; fax 972-3-655674.

EXPRESSION OF INTERMEDIATE FILAMENT PROTEINS IN THE ADULT HUMAN VESTIBULAR LABYRINTH

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The immunohistochemical detection of intermediate filament proteins, cytoskeletal constituents that allow the characterization of tissues, was investigated in frozen sections of the chemically fixed, nondecalcified, adult human vestibular labyrinth. Cytokeratins (CKs) were detected in all epithelia (including the sensory epithelia), although substantial differences in the degree of staining between individual cells occurred. The expression of CKs 7, 8, 18, and 19 as detected with our subunit-specific monoclonal antibodies in the vestibular epithelia is typical of "simple" epithelia and is identical to the CK subtypes found in the human cochlea. Although immunostaining for CK 7 was very weak and was limited to certain vestibular wall cells, the other CKs demonstrated a pronounced and rather uniform distribution throughout the different epithelia. All epithelia (including the sensory epithelia) displayed expression of vimentin, thus demonstrating co-expression with CKs. Vimentin was also present in the subepithelial connective tissue fibroblasts and mesothelial lining of the vestibular labyrinth. Neurofilament proteins were detected in all neuronal structures. The intense staining for CKs in the maculae and cristae implies that these sensory organs are rigid structures, a finding that may possibly be of importance in the mechanoelectrical transduction process for the sense of equilibrium.

KEY WORDS — adult human vestibular labyrinth, immunohistochemistry, intermediate filament proteins.

INTRODUCTION

Intermediate filament proteins (IFPs), together with microtubules and microfilaments, are prominent constituents of the cytoskeleton. An important feature of the main cytoplasmic classes of IFPs — cytokeratins (CKs), vimentin, desmin, glial fibrillary acidic protein (GFAP), and neurofilament proteins — is their tissue-specific distribution. In principle, in the mature vertebrate, a family of 20 different CKs is expressed by different types of epithelia, desmin is specifically expressed by muscle, vimentin by several cell types of mesenchymal origin, GFAP mainly by astroglia, and neurofilament proteins by neuronal cells.¹⁻³ However, combinations of up to three of these different IFPs can occur in certain tissues, especially during embryogenesis.³ Furthermore, different epithelia have been found to express different combinations of CKs depending on their nature and state of differentiation.⁴⁻⁶ Thus, it has become clear that the IFP composition of a cell may reflect both its embryonic origin and its functional state.

Moll et al⁴ have recently published an updated version of their catalog of human CKs and designated them 1 to 20, adding a newly detected CK to the former group of 19 constituents. They can be divided into two distinct families depending on their isoelectric pH, and it has been shown that

most basic (type II) CKs (numbers 1 through 8) form a pair with a specific acidic (type I) CK counterpart (numbers 9 through 20).^{4,5} Such pairs occur in cell type-specific combinations, while a clear correlation has also been found between the complexity of an epithelium ("simple" versus stratified versus "complex" epithelia) and the type of CK expressed. Simple epithelia express two to four of the group of CKs 7, 8, 18, and 19. Stratified epithelia express CKs 5 and 14/15, combined with one or more of the group of CKs 1, 2, 3, 4, 10, 12, and 13, depending on the differentiation program (skin, corneal, or esophageal type). Finally, complex or mixed epithelia such as glandular epithelia containing both basal and luminal cells, transitional epithelia, and pseudostratified epithelia usually express a mixture of simple and stratified types of CK polypeptides.^{5,6}

Various polyclonal and monoclonal antibodies to different IFPs have been developed, thus enabling the immunohistochemical characterization of tissues with respect to these cytoskeletal constituents. In addition, monoclonal antibodies that recognize epitopes unique to single CKs allow the immunohistochemical classification of different epithelia.

During the last decade, virtually all types of human tissues have been investigated for their expression of IFPs. The inner ear, however, was initially only investigated in animal species.⁷⁻¹² Because of

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technical difficulties encountered in human inner ear immunohistochemistry,¹³ data on the adult human vestibular labyrinth are still lacking. Intermediate filament protein data on the adult human cochlea have only just become available.¹⁴⁻¹⁶ Recently, studies have been published on IFP expression in the embryonic human inner ear, including the vestibular labyrinth.¹⁷⁻¹⁹ These results do, however, only allow limited conclusions with respect to its adult counterpart, since it is well known that tissues in developing embryos may express combinations of IFPs different from those in mature tissue.³ In fact, our earlier findings demonstrated major differences between IFP data in the adult human cochlea¹⁵ and previous results in human embryos.¹⁸

The aim of the present study was to immunohistochemically characterize the various tissues in the adult human vestibular labyrinth by investigating their IFP expression patterns. For this purpose, we used a previously described tissue processing technique that allows the reliable immunohistochemical detection of these structural proteins on frozen sections of the chemically fixed, nondecalfied, adult human inner ear.¹³

MATERIALS AND METHODS

Tissue Preparation. Temporal bones ($n = 10$) of five human adults (age 59 to 76 years) without a known history of inner ear disorders were fixed within 3 hours after death by perilymphatic perfusion with acetone (100%) for 10 minutes followed by perfusion with phosphate-buffered saline (PBS). After removal of the temporal bones at autopsy, the bony vestibule and semicircular canals were exposed by dissection of the surrounding bone. Subsequently, these inner ear structures were microdissected, essentially as described by Hawkins and Johansson.²⁰ Osmium tetroxide postfixation was omitted because of its known deleterious effects on the immunodetectability of certain antigens. In order to maintain the tissues in optimal condition and to prevent drying of the membranous labyrinth, the entire procedure was performed in cold PBS (4°C). After removal of the bony capsule, the vestibular part of the membranous labyrinth was removed in toto from the remnants of the bony labyrinth. After this, the specimens were embedded in Tissue-Tek II and cryosectioned.¹³

Antisera. Sections were incubated with polyclonal rabbit and monoclonal mouse antibodies to five classes of intermediate filament proteins, ie, vimentin, neurofilament proteins, desmin, GFAP, and different CK subunits. Unless indicated otherwise, antibodies were obtained from Euro-Diagnostics BV (Apeldoorn, the Netherlands). The CK subunit classification used in this paper is according to Moll et al.⁴

Cytokeratins were detected with the following

antibodies: monoclonal antibodies 6B10 (dilution 1:1, directed to CK 4), RCK 102 (dilutions 1:2.5 to 1:5, directed to CKs 5 and 8), RCK 105 (dilutions 1:1 to 1:5, directed to CK 7), M20 (dilutions 1:5 to 1:20, directed to CK 8), RKSE 60 (dilution 1:1, directed to CK 10), and 1C7 (dilution 1:1, directed to CK 13). Both RPN 1162 (dilutions 1:1 to 1:2.5, directed to CK 7) and RPN 1165 (dilutions 1:5 to 1:20, directed to CK 19) were obtained from Amersham International (England). Finally, the recently described monoclonal antibodies RCK 107 (dilution 1:1, directed to CK 14)²¹ and RCK 106 (dilutions 1:1 to 1:2.5, directed to CK 18)²² were used.

Vimentin was detected with the monoclonal antibody RV 202 (dilutions 1:200 to 1:600).²³

For detection of the neurofilament proteins, three monoclonal antibodies were used, ie, MNF (dilutions 1:10 to 1:20, directed to the 68/200 kd subunits), RNF 402 (dilutions 1:5 to 1:20, directed to the 200 kd subunit), and RNF 403 (dilutions 1:1 to 1:5, directed to the 160 kd subunit).

Desmin and GFAP were detected with polyclonal and monoclonal antibodies to desmin (PDE, dilutions 1:150 to 1:300; MDE, dilutions 1:1 to 1:2.5) and GFAP (PGF, dilutions 1:400 to 1:800; MGF, dilutions 1:1 to 1:1.5).

Immunolabeling. Cryosections (4 to 5 μ m) were air-dried at room temperature (15 minutes), fixed in 100% acetone (3 minutes), and air-dried once more. After washing in PBS the specimens were incubated with 10% normal goat serum (NGS; X 902, Dakopatts Corp, Glostrup, Denmark) in PBS for 20 minutes in order to diminish nonspecific binding. The sections were then incubated with the primary antibodies at the appropriate dilutions in 10% NGS for 30 minutes. After washing in PBS, the sections were incubated for another 30 minutes with the secondary antibodies, ie, rabbit anti mouse immunoglobulin G conjugated to peroxidase (P 260, Dakopatts Corp) for detection of monoclonal antibodies or swine anti rabbit IgG conjugated to peroxidase (P 217, Dakopatts Corp) for detection of polyclonal antibodies, diluted in 10% NGS. 3-Amino-9-ethyl-carbazole served as a chromogen for the peroxidase reaction. Finally, sections were counterstained with Mayer's hemalum, mounted in Kaiser's glycerol gelatin, and examined by light microscopy.

Appropriate human positive control tissues (including brain, peripheral nerve, muscle, liver, epidermis, tongue, esophagus, etc) were included to prove the specificity of the antibodies used. Negative controls were obtained by replacement of the primary antibody by either PBS or tissue culture medium (RPMI 1640, 10% fetal calf serum).

RESULTS

Tissue morphology was well preserved in all spec-

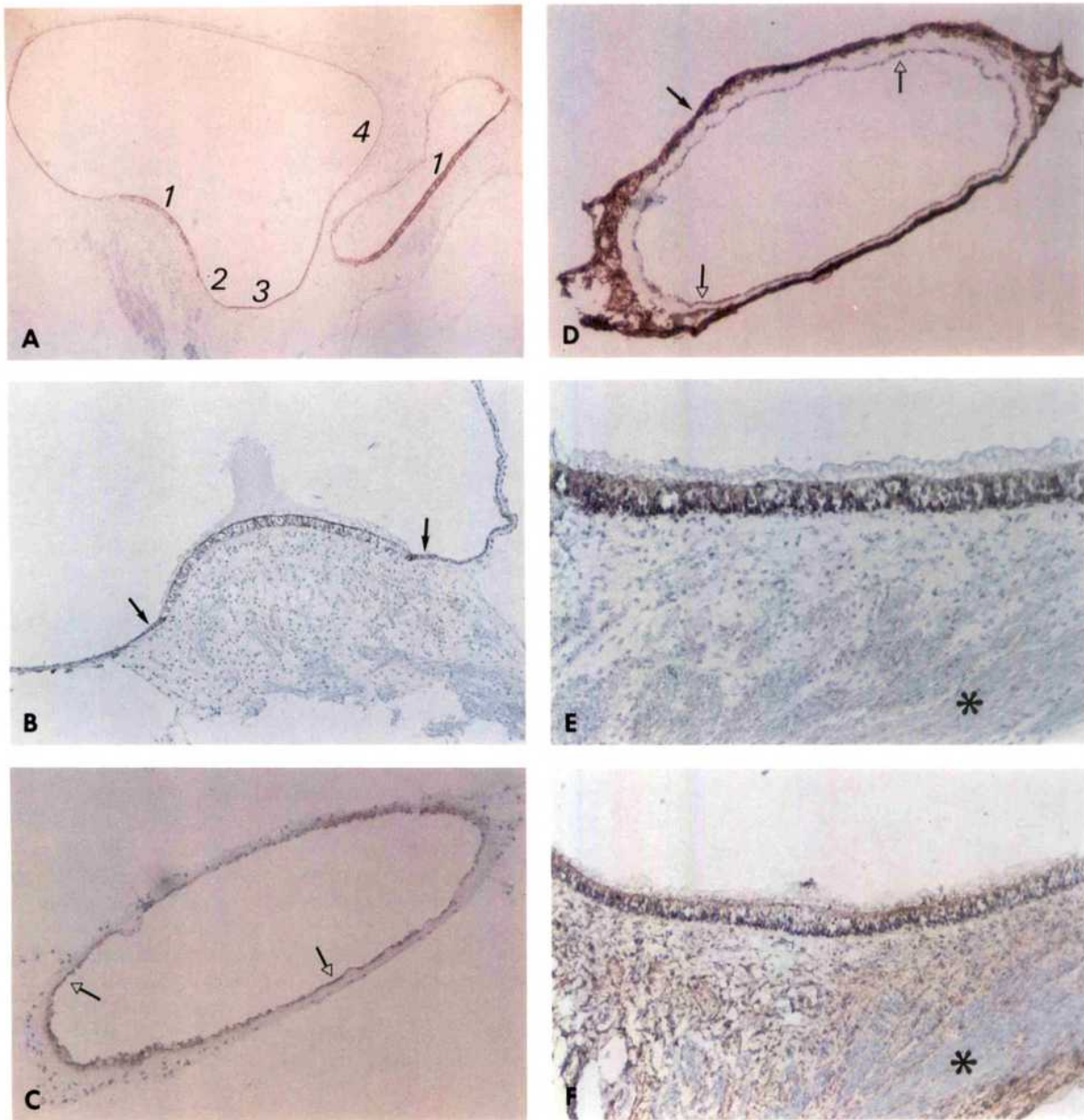


Fig 1. Immunostaining of vestibular labyrinth. A) Crista ampullaris and macula utriculi, immunostained with monoclonal antibody RPN 1165 to cytokeratin 19 (original x20). Shows intense immunoreactivity of sensory epithelia of crista and macula (1), moderate staining of transitional epithelium (2), region of dark cell epithelium (3), and vestibular wall cells (4). B) Crista ampullaris, immunostained with monoclonal antibody RCK 102 to cytokeratins 5 and 8 (original x50). Immunostaining is seen not only in sensory epithelium, but also in adjacent cuboidal or transitional cells (arrows). C) Cross section through semicircular canal, immunostained with monoclonal antibody RPN 1165 to cytokeratin 19 (original x70). Immunoreactivity only of vestibular wall cells lining endolymphatic space (arrows). D) Cross section through semicircular canal, immunostained with monoclonal antibody RV 202 to vimentin (original x70). There is intense immunostaining of mesenchymal cells on perilymphatic side (filled arrow), whereas vestibular wall cells (lining endolymphatic space) demonstrate only moderate immunoreactivity (open arrows). E) Macula utriculi, immunostained with monoclonal antibody RCK 102 to cytokeratins 5 and 8 (original x120). There is intense staining of sensory epithelium. Note absence of staining in statoconial layer, in subepithelial connective tissue, and in neural bundles (asterisk). F) Macula utriculi, immunostained with monoclonal antibody RV 202 to vimentin (original x100). There is intense immunostaining of sensory epithelium. Subepithelial fibroblasts also demonstrate immunoreactivity, whereas neural bundles (asterisk) and statoconial layer lack immunostaining.

imens (Figs 1-4). Most epithelial cell types (ie, the sensory epithelia of both cristae and maculae, the cuboidal cells or so-called "transitional cells" adjacent to these sensory epithelia, the dark cell epithelium, and the vestibular wall cells) could easily be

distinguished. However, cells of the planum semilunatum could not be clearly discerned, possibly because of the angle of sectioning. The ganglion cells of the vestibular (Scarpa's) ganglion were absent, since the tissue processing technique did not include

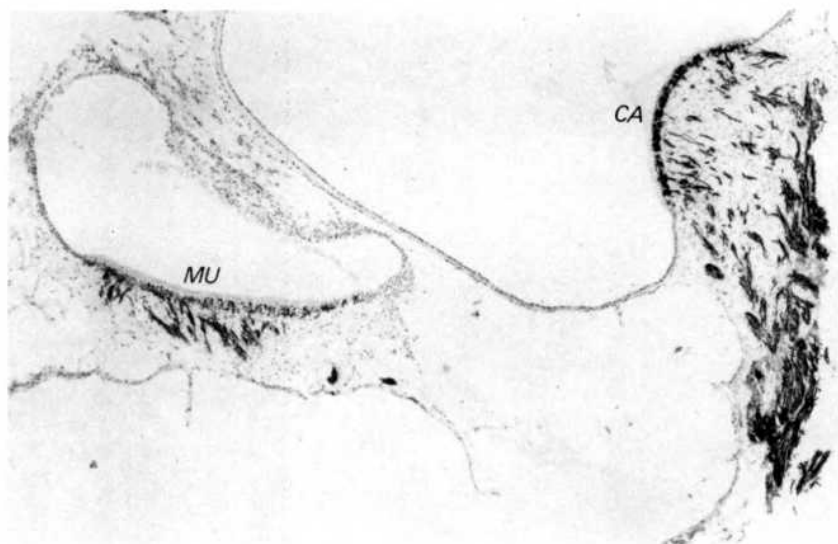


Fig 2. Crista ampullaris (CA) and macula utriculi (MU), immunostained with monoclonal antibody RNF 403 to neurofilament proteins (original x30). There is immunostaining of nerve fibers reaching sensory epithelia.

their site in the internal auditory canal.

All positive controls demonstrated specific immunostaining, thus proving the reactivity of the antibodies.

In all specimens immunostaining for the different antisera yielded similar results, differing only slightly in the degree of immunostaining. The staining patterns for the different antisera throughout the vestibular labyrinth are summarized in the Table and depicted in Figs 1-4.

Cytokeratins. Cytokeratins were detected in all distinguishable epithelial cell types lining the endolymphatic space of the vestibular labyrinth. Positive immunostaining with CK antibodies was found in the following epithelial cell types: the cells of the sensory epithelia of the maculae and cristae, which demonstrated intense immunostaining; the cuboidal or "transitional" cells adjacent to these sensory epithelia; the dark cell epithelium; and the vestibular wall cells of both the vestibulum and the semicircu-

lar canals (Fig 1A-C). However, all reactive antibodies demonstrated substantial differences in the degree of immunostaining (ranging from positive to negative) between adjacent, otherwise morphologically identical epithelial cells, especially in the non-sensory regions.

No immunostaining was observed with antibodies 6B10 (CK 4), RKSE 60 (CK 10), IC7 (CK 13), and RCK 107 (CK 14). Immunostaining for CKs 8, 18, and 19 in the sensory epithelia of the maculae and cristae was most intense in the basal region and at the apical surface of the epithelium (Fig 1B,E). However, it could not be discerned clearly at the light microscopic level whether immunostaining was confined to either the sensory cells or the sensory supporting cells, or was present in both these cell types. The transitional epithelium and dark cell epithelium were also positive for CKs 8, 18, and 19 (Fig 1A,B). The vestibular wall cells of the vestibulum showed positivity for CKs 7, 8, and 19 (Fig 1A), but strikingly did not for CK 18 as detected

Fig 3. Crista ampullaris, immunostained with monoclonal antibody MNF to neurofilament proteins (original x75). There is immunostaining of nerve fibers reaching sensory epithelium.

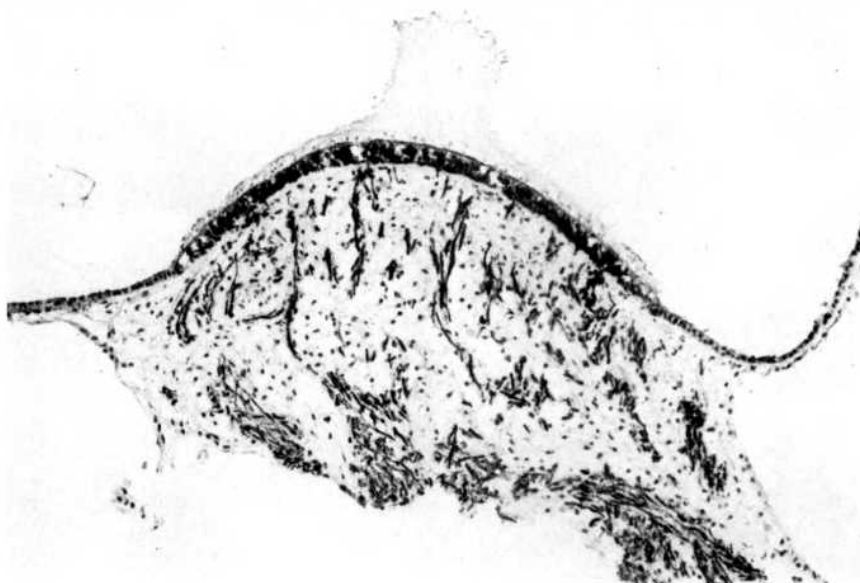
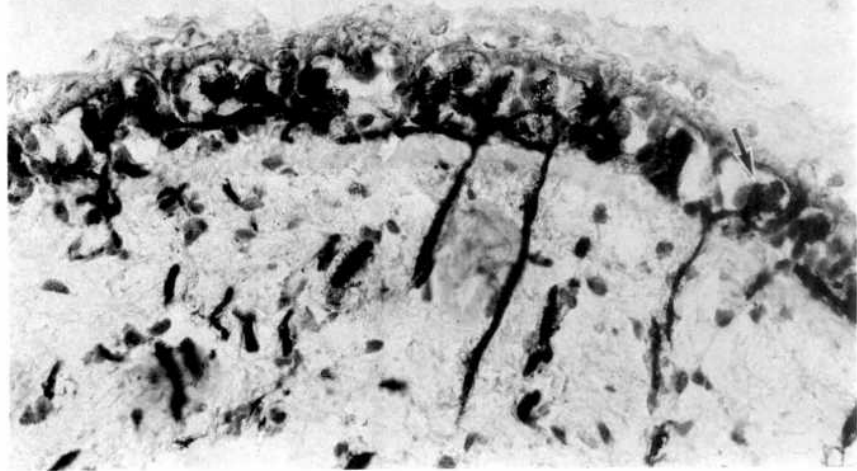


Fig 4. Detail of sensory epithelium of crista ampullaris, immunostained with monoclonal antibody RNF 403 to neurofilament proteins (original x300). Positively staining nerve fibers are seen penetrating into epithelium, after which they branch into smaller fibers. Staining of nerve calyces surrounding type I hair cells can be seen (arrow).



with antibody RCK 106. Even more striking was the finding that in our hands, in the vestibular wall cells of the semicircular canals only CK 19 could be detected (Fig 1C). Both monoclonal antibodies to CK 7 (ie, RCK 105 and RPN 1162) revealed only very weak staining, limited to certain epithelial cells adjacent to the dark cell epithelium that were interpreted as vestibular wall cells. Immunostaining for CKs was absent in all other (nonepithelial) regions of the membranous labyrinth, including such extracellular structures as the cupulae and the statoconial layers of the maculae.

Vimentin. Immunostaining for vimentin was present in the subepithelial connective tissue fibroblasts and mesothelial lining (on the perilymphatic side) of the membranous labyrinth (Fig 1D,F). Staining also occurred in all epithelial cell types bordering the endolymphatic space, including the cells of the sensory epithelia of the maculae and cristae (with insufficient resolution to differentiate between sensory supporting cells and sensory cells; Fig 1F), the cuboidal (transitional) cells bordering these sensory epithelia, the dark cell epithelium, and the vestibular wall cells of both the vestibulum and the semicircular canals (Fig 1D). However, again a considerable variation in immunostaining between individual, otherwise identical, epithelial cells occurred as described with CK staining. Immunostaining was absent in the nerve fibers reaching the sensory epithelia and in the cupulae and statoconial layers of the sensory organs (Fig 1F).

Neurofilament Proteins. All monoclonal antibodies to neurofilament proteins revealed identical staining results. Immunostaining occurred in the nerve fibers reaching the sensory epithelia of the maculae and cristae (Figs 2 and 3). Figure 4 shows neurofilament reactivity in the nerve endings at the sensory cells, including the nerve calyces surrounding the type I hair cells.

Desmin and GFAP. All antibodies to these intermediate filament proteins lacked immunostaining.

DISCUSSION

In this study we have demonstrated the presence of CKs, vimentin, and neurofilament proteins in the adult human vestibular labyrinth, whereas desmin and GFAP were absent. Using monoclonal antibodies to different CK polypeptides, we demonstrated the presence of CKs 7, 8, 18, and 19 in the epithelia of the vestibular labyrinth, while CKs 4, 10, 13, and 14 could not be identified with our antisera. However, since biochemical analysis was not performed in support of negative immunohistochemical findings, absence of staining (desmin, GFAP, and certain CK subunits) does not definitely exclude the presence of the IFPs concerned, and the results are therefore to be interpreted with caution.

Our present immunohistochemical results on CK expression confirm in general earlier, albeit more limited, data on the embryonic human inner ear.¹⁷⁻¹⁹ In addition, the CK-positive staining of all cell types lining the endolymphatic space of the vestibular labyrinth supports the generally accepted epithelial origin of these cells. However, it is not clear whether the differences in immunostaining between adjacent, morphologically otherwise similar, individual cells reflect true differences in their CK composition, since we are well aware of the fact that epitope masking may occur.²²

Cytokeratin staining of the different cell types in the sensory epithelia of the maculae and cristae, ie, sensory supporting cells and sensory cells, remains controversial. In two subsequent studies on human embryos, Thornell et al¹⁷ and Anniko et al¹⁹ reported immunoreactivity to exist either in both cell types¹⁹ or only in the supporting cells.¹⁷ In the present study, insufficient resolution of our immunohistochemical technique in the different sensory epi-

OVERALL STAINING PATTERNS FOR DIFFERENT INTERMEDIATE FILAMENT PROTEIN ANTISERA THROUGHOUT VESTIBULAR LABYRINTH

	Sensory Epithelium Maculae	Sensory Epithelium Cristae	Tran- sitional Epithelium	Dark Cell Epithelium	Vestibular Wall Cells of Vestibulum	Vestibular Wall Cells of Semi- circular Canal	Subepi- thelial Connective Tissue	Nerve Fibers and Nerve Endings	Mesothelial Lining	Extra- cellular Structures*
Cytokeratins										
6B10 (CK 4)	—	—	—	—	—	—	—	—	—	—
RCK 102 (CKs 5 and 8)	+	+	+	+	+	—	—	—	—	—
RCK 105 (CK 7)	—	—	—	—	+†	—	—	—	—	—
RPN 1162 (CK 7)	—	—	—	—	+†	—	—	—	—	—
M20 (CK 8)	+	+	+	+	+	—	—	—	—	—
RKSE 60 (CK 10)	—	—	—	—	—	—	—	—	—	—
IC7 (CK 13)	—	—	—	—	—	—	—	—	—	—
RCK 107 (CK 14)	—	—	—	—	—	—	—	—	—	—
RCK 106 (CK 18)	+	+	+	+	—	—	—	—	—	—
RPN 1165 (CK 19)	+	+	+	+	+	+	—	—	—	—
Vimentin										
RV 202	+	+	+	+	+	+	+	—	+	—
Neurofilaments										
MNF	—	—	—	—	—	—	—	+	—	—
RNF 402	—	—	—	—	—	—	—	+	—	—
RNF 403	—	—	—	—	—	—	—	+	—	—
Glial fibrillary acidic protein										
PGF	—	—	—	—	—	—	—	—	—	—
MGF	—	—	—	—	—	—	—	—	—	—
Desmin										
PDE	—	—	—	—	—	—	—	—	—	—
MDE	—	—	—	—	—	—	—	—	—	—

*Cupulae and statoconial layers.

†Weak immunostaining in sporadic cells.

thelia prevented definite conclusions on this matter. However, we demonstrated a particularly intense immunoreactivity for CKs along the surface and in the basal regions of the sensory epithelia of the maculae and cristae. This pattern greatly resembles the staining patterns for CKs in the other neuroepithelial structure of the inner ear, the organ of Corti, in which staining was also most intense in the basal and apical regions. In this structure, CKs were demonstrated exclusively in the various supporting cells and not in the hair cells.¹⁵ Because the basal regions of the vestibular sensory epithelia of the maculae and cristae mainly contain the cell bodies of the sensory supporting cells, our finding of intense staining in this region suggests positive staining of at least this cell type. Immuno-electron microscopic studies are needed to elucidate the exact CK distribution pattern in the vestibular sensory epithelia.

Since it has become generally accepted that CKs at least partially mediate the stiffness of tissues,²⁴ our finding of intense immunostaining for CKs in

the sensory epithelia of the maculae and cristae suggests that these sensory organs may be rigid structures. This cellular rigidity may then be considered to be of importance in the mechanoelectrical transduction process for the sense of equilibrium, possibly by opposing the motion of the cupulae and statoconial layers.

The application of monoclonal antibodies to different CK subunits enables the differentiation of epithelia by means of their CK expression pattern. In this study we used monoclonal antibodies that are monospecific for CKs 4, 7, 8, 10, 13, 14, 18, and 19, thus including markers for simple, stratified (among them keratinizing), and complex epithelia as outlined in the Introduction. We show in this study that the vestibular epithelia contain CKs 7, 8, 18, and 19, which are characteristic of simple or single-layered epithelia. The same CK subtypes have recently been demonstrated in the adult human cochlea.¹⁶ However, in the adult human endolymphatic duct and sac, CKs typical of complex epi-

thelia were found, since in this part of the inner ear the additional presence of CKs 14 and 17 was demonstrated.²⁵

A further classification of simple epithelia on the basis of their CK pattern is generally not possible, since similar patterns are common to multiple functionally heterogeneous simple epithelia.¹⁶

All CKs other than CK 7 were found to have a rather uniform distribution in the different epithelial cell types of the vestibular labyrinth. However, the vestibular wall cells of both the vestibulum and the semicircular canals demonstrated considerable differences in their immunoreactivity to different CK antibodies. It is, however, uncertain whether these staining results represent true differences in CK composition or whether they reflect artifacts due to antigenic masking or to differences in the affinity of the antibodies concerned.

The possibility of false-negative results due to epitope masking with our two different antibodies to CK 7, however, is not conceivable, since these antibodies were obtained from different fusions and are therefore likely to recognize different epitopes. However, although results with both antibodies were identical, immunostaining was so weak that we are reluctant to draw any conclusions as to a possible differential expression of CK 7 in the epi-

thelium of the vestibular labyrinth.

All epithelial cell types (including the sensory epithelia) expressed vimentin in addition to CKs, thus demonstrating coexpression of these IFPs. Interestingly, coexpression of CKs and vimentin has also been demonstrated in other parts of the adult human inner ear. In the cochlea, the pillar cells and Deiters' cells of the organ of Corti and the region of the spiral prominence and outer sulcus demonstrated coexpression of these IFPs,¹⁵ whereas in the endolymphatic duct and sac the entire epithelial lining demonstrated this phenomenon.²⁵

Although the finding of coexpression of CKs and vimentin enables a further characterization of tissues, its meaning is not yet understood. Coexpression of these two IFPs has been demonstrated in several human neuroepithelial tissues,²⁶ but has also been found in other epithelia and mesothelial cells.³

All neuronal structures were found to express neurofilament proteins only. We could not confirm earlier results on the coexpression of vimentin and neurofilament proteins in these neuronal structures as described in human embryos.¹⁷ This dissimilarity, which also existed between the adult¹⁵ and embryonic cochleas,¹⁸ may be due to the transient expression of vimentin, in addition to another IFP, in many tissues during embryonic development.

ACKNOWLEDGMENTS — The skilled technical assistance and devotion of I. C. Bihari is gratefully acknowledged. The authors also thank J. Kuipers-van der Giessen and F. Meeuwssen for their collaboration during this study. Finally, we are indebted to W. Kuijpers for his advice on vestibular morphology.

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PRIMARY SALIVARY GLAND AMYLOIDOSIS CAUSING SICCA SYNDROME

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Sicca syndrome (SS), consisting of xerostomia and xerophthalmia, may be caused by various disease processes. We present a unique case of SS secondary to primary amyloidosis. Amyloidosis is a rare but definite cause of SS and should be included in the differential diagnosis of any patient who presents with sicca symptoms. A literature review comparing amyloidotic patients with SS and patients with amyloidosis only demonstrates that both of these groups of patients present similarly with regard to symptoms. However, the majority of patients with SS present with sicca symptoms initially in addition to symptoms of amyloidosis. These SS patients also present with proteinuria and negative serology test results. Therefore, patients presenting with sicca symptoms, proteinuria, and negative serologic findings should be suspect for amyloidosis. The importance of distinguishing the diagnosis of Sjögren's syndrome from SS in these patients cannot be overemphasized. There is a significantly higher incidence of developing a lymphoma in Sjögren's syndrome patients. This has important implications for the head and neck surgeon treating these patients.

KEY WORDS — amyloidosis, bilateral parotid gland enlargement, parotid gland, sicca syndrome, Sjögren's syndrome.

CASE REPORT

A 74-year-old woman presented with intermittent, bilateral parotid swelling that occurred over a 15-year period (Fig 1). Over the last year her glands had become firmer and larger. Her parotid glands did not enlarge with eating. There was no associated history of starch consumption, alcohol abuse, antiepileptic medication use, or tobacco abuse. She also complained of dry eyes and oral dryness that required ocular lubricants and frequent drinks of water, respectively. She denied joint pain, rash, arthritis, and shortness of breath. She took no medications and was allergic to penicillin, codeine, and topical steroids.



Fig 1. Patient with bilaterally enlarged parotid glands.

The patient had a tonsillectomy as a child and a tubal ligation.

Findings on general physical examination were normal, with no evidence of organomegaly or cardiomegaly and normal breath sounds. Her ears, nose, and nasopharynx were normal. A positive Schirmer's response was elicited bilaterally (1 mm over 5 minutes). Her saliva production was poor and her mucous membranes were dry. Her parotid glands were firm, nontender, and mobile and measured 6 x 5 cm each. The submandibular glands were firm but not enlarged.

Laboratory examination included a white blood cell count of 5.2, hemoglobin of 13.9, an erythrocyte sedimentation rate of 18 mm/h, and a normal Sequential Multiple Analysis reading of 20 chemical constituents. Antinuclear antibodies, Sjögren's syndrome A antigen (SS-A), and Sjögren's syndrome B antigen (SS-B) were normal. The patient was weakly positive for serum rheumatoid factor (1:40). Serum protein electrophoresis results were normal except for a slight elevation of her gamma globulins (1.9 g/dL; 0.7 to 1.5 is normal range). There was no proteinuria. Results of her chest radiograph and electrocardiogram were noncontributory.

A sublabial biopsy of a minor salivary gland revealed glandular acini surrounded by an amorphous, acellular material on hematoxylin and eosin staining (Fig 2A). Under polarized light, there was intense

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Presented at the meeting of the American Laryngological, Rhinological and Otolological Society, Philadelphia, Pennsylvania, January 31–February 2, 1991.

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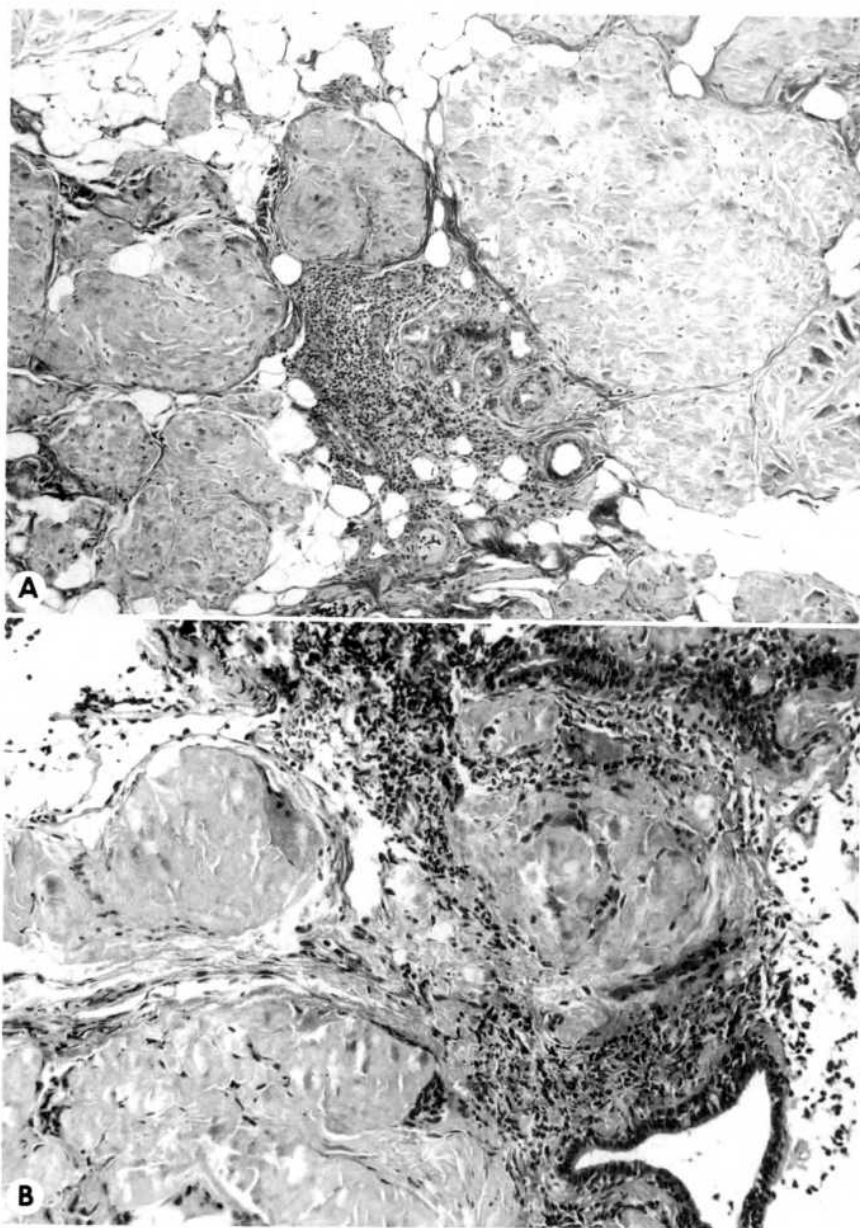


Fig 2. Biopsies (H & E, original x200). A) Of lip, showing nodular homogeneous deposits of amyloid surrounding minor salivary gland and extending into fat. B) Of parotid gland that is being replaced by amyloid deposits and has dilated residual ducts and scant salivary tissue.

birefringence after Congo red staining. There was little evidence of lymphocytic infiltration.

Because her SS-A and SS-B were negative and her lip biopsy did not support Sjögren's syndrome, a fine-needle aspiration biopsy of her parotid gland was performed with appropriate staining. This was inconclusive; hence, a Tru-Cut biopsy specimen of her parotid gland was obtained (Fig 2B). This biopsy also revealed atrophic acini surrounded by amorphous material that was birefringent after Congo red staining.

The patient was referred to a rheumatologist for further evaluation. One year later she remains unchanged with no advanced symptoms of amyloidosis.

DISCUSSION

Sicca syndrome (SS), consisting of xerostomia and xerophthalmia, affects countless patients in the United States. The prevalence is unknown, but it is probably at least as common as rheumatoid arthritis (approximately 1%). It may be caused by Sjögren's syndrome, sarcoidosis, or acquired immunodeficiency syndrome. Our patient illustrates that although rare, salivary gland infiltration by amyloid is a definite cause of SS and should be included in the differential diagnosis of patients presenting with xerostomia and xerophthalmia.

Amyloidosis is a definite cause of SS, not to be confused with Sjögren's syndrome. The incorrect presumption that all patients with SS have Sjögren's syndrome has probably resulted from the confusion

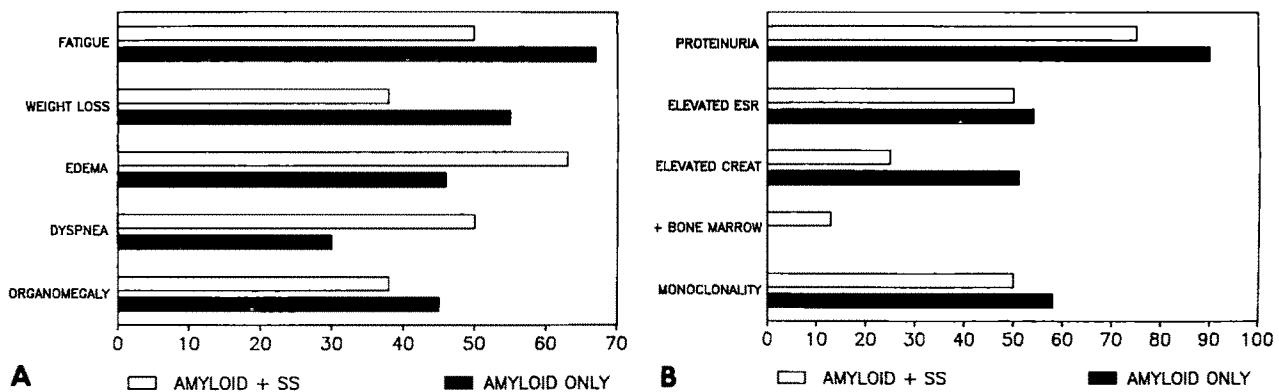


Fig 3. Findings from this study and literature^{2,10-18} on patients with amyloidosis with and without sicca syndrome (SS). A) Symptoms. B) Laboratory data. ESR — erythrocyte sedimentation rate, Creat — creatinine, + Bone Marrow — presence of myeloma cells, Monoclonality — presence of κ or λ immunoglobulin light chains.

in the literature regarding the definition of Sjögren's syndrome. Well-defined criteria for the classification of Sjögren's syndrome have not been established. Fox et al¹ have proposed criteria for the diagnosis of Sjögren's syndrome based on a common etiopathogenesis. Because clinical symptoms may not be specific enough to allow a diagnosis of Sjögren's syndrome,² their criteria are based on objective evidence. According to these authors, definite Sjögren's syndrome is diagnosed only after all four criteria are met: 1) objective evidence of keratoconjunctivitis sicca, 2) objective evidence of diminished salivary gland flow, 3) minor salivary gland biopsy of a specimen containing at least four salivary gland lobules, and 4) evidence of a systemic autoimmune process.

It has been suggested that labial salivary gland biopsy is a more disease-specific feature of Sjögren's syndrome than xerostomia or any other feature of salivary disease.² Some series have reported diagnostic biopsies ranging from 68% to 81% in patients with Sjögren's syndrome.^{3,4} However, 36% of patients with connective tissue disease also had similar-appearing biopsies.

The importance of serology in the diagnosis of Sjögren's syndrome has been stressed.⁵ Both SS-A and SS-B are small-molecular weight ribonuclear proteins synthesized by RNA polymerase III.⁶ Sjögren's syndrome was found in 30 of 33 patients who had SS-A and/or SS-B antibodies (90% specificity).⁵

The importance of distinguishing between Sjögren's syndrome and SS caused by other diseases cannot be overemphasized. There have been reports in the literature of SS due to amyloidosis and Sjögren's syndrome confirmed by salivary gland biopsy.^{7,8} These patients are a distinctly different population from patients with SS secondary to amyloidosis without simultaneous Sjögren's syndrome. It has been

estimated that there is an incidence of lymphoma 48.3 times higher than expected, in patients with Sjögren's syndrome.⁸ This has important surgical implications for the head and neck surgeon.⁹

Amyloidosis is a disease of unknown cause in which a pathologic proteinaceous substance is deposited between cells in various tissues of the body with progressive accumulation. This material produces pressure atrophy leading to dysfunction of tissue and hence to various pathologic states, ie, congestive heart failure, renal failure, macroglossia, and SS. Diagnosis can be made by skin, rectal, or salivary gland biopsy. Histologically, amyloid is birefringent under polarized light when stained with Congo red. Therapy for amyloidosis is palliative and organ-directed.

Including the present case, there are 10 case reports of SS due to primary amyloidosis in the English-language literature.^{2,10-17} In a comprehensive review of patients with primary amyloidosis without myeloma, Kyle and Bayrd¹⁸ discovered certain characteristics common to this group of patients. We analyzed eight cases (including the present one) of amyloidosis and SS with adequate documentation with respect to the aforementioned criteria¹⁸ (Fig 3A^{2,10-18}).

This population of amyloidotic patients with SS shared many similarities with the amyloid patients lacking SS. The SS patients showed no sex preponderance and presented most commonly with edema, fatigue, and dyspnea. Eighty-five percent of these SS patients presented initially with sicca symptoms in addition to the above-mentioned symptoms. Our patient is unique in that she presented with SS only and no other symptoms. Although it is tempting to state that sicca symptoms may be an early indication of primary amyloidosis and that our patient received her diagnosis in an early stage of the disease, this is speculation.

Figure 3B illustrates that proteinuria and the presence of a monoclonal protein (λ or κ light chains) were common in the group of amyloid patients with SS. That 87% of these sicca patients had no positive serology tests is consistent with the diagnosis of primary, as opposed to secondary, amyloidosis.¹⁴ Although the symptoms of patients with SS due to primary amyloidosis are similar to those of amyloidotic patients without SS, patients with SS initially present with xerophthalmia and xerostomia in addition to other symptoms. Patients presenting with sicca symptoms, proteinuria, and negative serologic testing should be suspected for amyloidosis.

Other types of amyloidosis have presented as SS. Three cases of SS due to secondary amyloidosis have been reported.¹⁹⁻²¹ Amyloidosis in these cases was

secondary to rheumatoid arthritis. The familial amyloidoses have also been reported to cause SS.^{22,23} It is important to diagnose familial amyloidosis, since colchicine has been reported to be efficacious in the treatment of this type of amyloidosis.^{24,25} In addition, genetic counseling is advisable for these patients.

We have presented a rare case and literature review of SS secondary to primary amyloidosis of the salivary glands. These patients are similar to amyloidotic patients without SS except that they initially present with sicca symptoms, proteinuria, and negative serology. We emphasize that amyloidosis is a definite cause of SS and should be included in the differential diagnosis of patients presenting with sicca symptoms.

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PRESENCE OF AN 80 KILODALTON PROTEIN, CROSS-REACTED WITH MONOCLONAL ANTIBODIES TO PULMONARY SURFACTANT PROTEIN A, IN THE HUMAN MIDDLE EAR

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We report the presence of a middle ear protein that has the same epitope as human surfactant protein A. Monoclonal antibodies (PC-6 and PE-10) against human pulmonary surfactant protein A stained faint granules of the mucosal epithelial cell cytoplasm in the orifice of the eustachian tube immunohistochemically. These antibodies also reacted with middle ear effusion of patients with otitis media with effusion by dot immunoassay, and recognized an 80 kd protein by Western blot analysis. These findings indicate that a protein immunoreactive with PC-6 and PE-10 occurs in the mucosal epithelial cells of the middle ear, and is also present in middle ear effusion. It is therefore likely that this 80 kd protein might be secreted from the mucosal epithelial cells to the middle ear cavity.

KEY WORDS — eustachian tube, immunoassay, otitis media with effusion, surfactant protein A.

INTRODUCTION

The cause of otitis media with effusion has not been completely understood, but many studies indicate that dysfunction of the eustachian tube plays a role in its pathogenesis. The eustachian tube is normally closed, but frequently opens by contraction of the tensor veli palatini muscle during swallowing, yawning, or sneezing to adjust the middle ear pressure. The surface activity of the middle ear cavity has been attributed variously to the glycoproteins of the mucous blanket and to the phospholipids.^{1,2}

Birken and Brookler³ demonstrated a surface tension-lowering substance in washings from the canine eustachian tube and suggested that such a surfactantlike substance might facilitate opening of the eustachian tube.

Kuroki et al⁴ developed monoclonal antibodies to human surfactant protein A (SP-A), a 28 to 38 kd glycoprotein, and the antibodies to this glycoprotein have been used immunohistochemically as a marker of pulmonary surfactant. Although it is still uncertain whether the surfactantlike substance in the eustachian tube is the same substance as the main component of pulmonary surfactant, in the present study we performed an immunohistochemical analysis of the human middle ear mucous membrane and effusion using a monoclonal antibody to SP-A. The results showed the presence of an 80 kd protein in the middle ear cavity that cross-reacted with the antibodies to human SP-A.

obtained from adults and infants at autopsy. Post-mortem time was within 6 hours. The mucous membrane of the middle ear cavity was removed from these temporal bones and was fixed with 10% formalin solution for 7 days.

The avidin-biotin-peroxidase complex method was employed in this study as the immunostaining procedure. Paraffin sections of mucous membranes, 4 μ m thick, were deparaffinized with xylol and washed three times in cold phosphate-buffered saline (PBS), pH 7.4, for 5 minutes each. The sections were incubated in 0.6% H₂O₂ in methanol for 30 minutes at room temperature for inhibition of endogenous peroxidase and then were washed with PBS, pH 7.4, at 4°C.

The sections were incubated with monoclonal antibody (PC-6 or PE-10), which was developed against human pulmonary surfactant,⁴ for 30 minutes at room temperature and then washed with PBS. The sections were incubated with biotin-labeled goat anti mouse immunoglobulin antibodies (Vector Laboratories, Burlingame, Calif) for 30 minutes at room temperature, and then were washed with PBS. Then 1:200-diluted fresh avidin D-biotinylated horseradish peroxidase solution (Vector Laboratories) was applied for 30 minutes at room temperature.

After washing with PBS, all sections were reacted with a substrate of 0.03% 3-3' diaminobenzidine in 0.05 mol/L TRIS buffer, pH 7.4, with 0.03% hydrogen peroxide for 2 to 5 minutes at room temperature. The sections were counterstained with hematoxylin or methyl green.

MATERIALS AND METHODS

Immunohistochemistry. The temporal bones were

Dot Enzyme Immunoassay. Dot enzyme immu-

From the Department of Otolaryngology (Kobayashi, Yamanaka, Kataura), the Central Histology Laboratory (Ohtani), and the Department of Biochemistry (Saito, Akino), Sapporo Medical College, Sapporo, Japan.

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Fig 1. Immunoperoxidase staining (PE-10) of human middle ear cavity. A) Section of tympanic cavity shows positive staining of surface of mucosal epithelial cell (original $\times 1,175$). Granular products (arrows) are seen in cytoplasm of mucosal epithelial cells in orifice of eustachian tube. B) Section of normal adult lung shows positive staining of alveolar wall for PE-10 (original $\times 470$). Granular products are seen in cytoplasm of type II cells that protrude into alveoli (arrowheads).

noassay was carried out for screening of antigen. This immunoassay was done according to the procedure of Hawkes et al.⁵ The principle of the assay is as follows. Middle ear effusions obtained from patients with otitis media with effusion were "dotted" onto a nitrocellulose sheet. After blocking the unbound site with 1% (wt/vol) skim milk (Snow brand, Sapporo, Japan) in PBS for inhibition of nonspecific antibody binding, the dots were first incubated with the monoclonal antibody (PC-6 or PE-10) for 2 hours and then washed three times with 1% skim milk.

Biotinylated horse anti mouse immunoglobulin G was then added on the sheet as a secondary antibody. Each sheet was washed in PBS containing 0.05% (vol/vol) Tween-20. After incubation with horseradish peroxidase-avidin D for 1 hour, substrate solution (0.05% diaminobenzidine, 0.03% hydrogen peroxide) was added. A positive reaction was detected as a colored dot against the white sheet background.

Western Blot Technique. We identified the antigen specific for the monoclonal antibodies using the Western blot technique by the method of Towbin et al.⁶ Five milliliters of chloroform-methanol (2/1) was added to 1.0 mL of the middle ear effusion. After mixing for 2 minutes in a vortex, the solution was centrifuged at 500g for 15 minutes. The upper

layer (methanol layer) was subjected to analysis.

The upper layer containing water-soluble antigens of human middle ear effusion was dried under nitrogen, then concentrated sample was subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The proteins were transferred to a nitrocellulose sheet from the slab gel after sodium dodecyl sulfate-polyacrylamide gel electrophoresis under conditions in which the electrode buffer was 2 nmol/L TRIS-hydrochloride (pH 8.3), 192 mmol/L glycine, 20% (vol/vol) methanol, and a voltage gradient of 7 V/cm had been applied for 2 hours. Each lane of the sheet was cut out. One lane was used for staining of proteins with Amido Black 10B, and the others were subjected to the enzyme immunoassay as mentioned above.

RESULTS

Immunohistochemical Studies With PC-6 and PE-10. The monoclonal antibodies (PC-6 and PE-10), which stained the cytoplasm of type II cells in the lung (Fig 1B), were used to stain proteins in the epithelial cells of the middle ear cavity immunohistochemically. Monoclonal antibodies (PC-6 and PE-10) against pulmonary SP-A faintly stained granules in the cytoplasm of some mucosal epithelial cells in the orifice of the eustachian tube, but not any of the secretory cells (Fig 1A). These monoclon-



Fig 2. Dot enzyme immunoassay for monoclonal antibody (PE-10) against surfactant protein A in middle ear effusion. Method is described in text. All dots of middle ear effusion showed positive staining with monoclonal antibody in various degrees. Both monoclonal antibodies (PC-6 and PE-10) against human surfactant protein A showed same results. 1,3,6 — mucoid effusion, 4 — purulent effusion, 2,5 — serous effusion.

al antibodies also reacted with the surface of both the tympanic cavity and the eustachian tube.

Identification of Antigen. Proteins present in the middle ear effusion were analyzed by dot enzyme immunoassay using monoclonal antibodies (PC-6 or PE-10). Monoclonal antibody (PC-6 or PE-10) was used as the primary antibody. Dot enzyme immunoassay showed various degrees of positive reaction to the middle ear effusion, showing the presence of proteins cross-reactive with human SP-A (Fig 2). Both monoclonal antibodies, PC-6 and PE-10, clearly recognized a protein band of molecular weight 80,000 (80 kd) in the middle ear effusion by the Western blot technique (Fig 3). No immunoreactivity was observed with 3% (wt/vol) of bovine albumin nor a nonspecific antimouse immunoglobulin G. These results showed that both PC-6 and PE-10 recognized the same protein.

DISCUSSION

The potential existence of a surface tension-lowering substance of the middle ear cavity facilitating the opening of the eustachian tube was first postulated by Bauer in 1970.⁷ Birken and Brookler³ compared the stability of bubbles formed in washings obtained from canine eustachian tubes and lungs. That the results were similar suggested that a substance analogous to lung surfactant was present in the eustachian tube. Rapport et al⁸ measured the pressure required to open the eustachian tube in the temporal bones of guinea pigs. These authors demonstrated that successive tubal openings became progressively easier, but irrigation of the tube with saline solution elevated the mean critical opening pressure by 55%, presumably by removal of "surfactant."

Hills¹ used thin-layer chromatography in order to measure the relative quantities of phospholipids in washings of the eustachian tube and lung lavage fluids from dogs and rabbits. Appreciable amounts of phospholipids were shown to be present in the eustachian tube washings, and the phospholipids exhibited significant activity in reduction of surface tension at the liquid-air interface. However, no direct evidence of the existence of surfactant within the human middle ear has been reported so far.

The major components of pulmonary surfactant

are phospholipids, especially dipalmitoyl phosphatidylcholine. However, there is evidence that specific proteins associated with surface-active phospholipids occur.⁹

Pulmonary surfactant-associated proteins, termed surfactant proteins A, B, and C, have been isolated

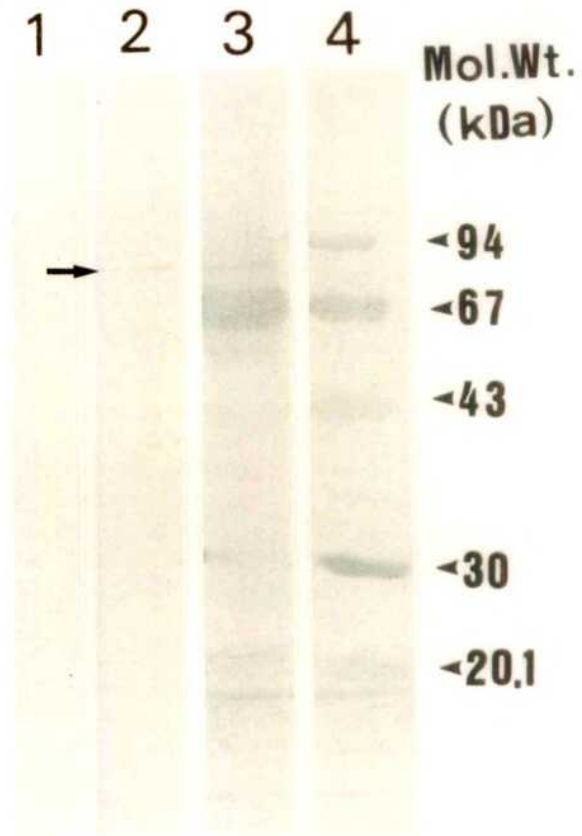


Fig 3. Sodium dodecyl sulfate gel electrophoresis and immunostaining of middle ear effusion (Western blot technique). After electrophoresis, proteins were electrophoretically transferred to nitrocellulose sheet. In tracks 1 and 4, standard marker protein, and in tracks 2 and 3, several proteins of middle ear effusion were transferred. In tracks 3 and 4, proteins were visualized by staining with Amido Black 10B. Proteins of middle ear effusion in track 2 were detected by enzyme immunoassay as described in text. Estimated molecular weight of proteins cross-reacted with monoclonal antibody (PC-6 or PE-10) was 80,000 (80 kd; arrow). In track 4, standard marker proteins are as follows: phosphorylase *b* (94 kd), bovine serum albumin (67 kd), ovalbumin (43 kd), carbonic anhydrase (30 kd), and soybean trypsin inhibitor (20.1 kd).

and purified from the lung lavages of various animals. Kuroki et al¹⁰ prepared monoclonal antibodies (PC-6 and PE-10) against human pulmonary SP-A. The antibodies recognized the same glycoproteins, ie, 62 and 36 kd proteins in the lavages of patients with alveolar proteinosis. They also recognized 37 kd and 34 kd proteins in human lung lavage and amniotic fluids. The epitope recognized by the antibodies is located in the C-terminal peptide portion of the human SP-A molecule (unpublished).

In the present study, monoclonal antibodies (PC-6 and PE-10) recognized an 80 kd protein in the middle ear effusion, the molecular weight of which was different from that of human SP-A. However, Bhattacharyya and Lynn¹¹ reported the presence of soluble glycoprotein of molecular weight 80,000 (80 kd) from lung lavages of patients with alveolar proteinosis. They found that this 80 kd glycoprotein resulted in four peptide fragments with molecular weights of 62,000, 36,000, 26,000, and 18,000 by chemical and enzyme treatments. In addition, the carbohydrate structures of these peptide fragments isolated from the 80 kd glycoprotein are identical to those of glycoproteins with molecular weights of 62,000 and 36,000 that were separated from lung lavage of patients with alveolar proteinosis. Bhattacharyya et al¹² also reported that these glycoproteins were found to be present in the lung of normal animals. Furthermore, antisera raised in rabbits against the glycoproteins with molecular weights of 62,000 and 36,000 reacted immunohistochemically with the 80 kd glycoprotein.¹¹

Recently, it has been demonstrated that the 36 kd glycoprotein present in the lung lavage fluids of patients with alveolar proteinosis is identical with pulmonary SP-A, and the 62 kd glycoprotein is a dimer of the 36 kd glycoprotein.^{13,14} Therefore, it is possible that the 80 kd protein that we detected in the middle ear effusion by immunoblotting with PC-6 or PE-10 might contain SP-A.

We also demonstrated in this study fine positive granules in the cytoplasm of the mucosal epithelial cell of the orifice of the eustachian tube by immunohistochemical study with monoclonal antibody (PC-6 or PE-10).

Other cell types, ie, goblet and secretory cells in

the middle ear, were not stained immunohistochemically. These findings indicate that the protein immunoreactive with monoclonal antibody (PC-6 or PE-10) occurs in a specific cell type of the mucosal epithelial cells of the middle ear as granules and in the middle ear effusion in water-soluble form. It is therefore likely that this 80 kd protein might be secreted from the mucosal epithelial cell to the middle ear cavity.

It seems likely from the numerous pieces of evidence mentioned above that surfactantlike substances are present in the middle ear and function to adjust the middle ear pressure. The pulmonary surfactant is mainly composed of phosphatidylcholine, predominantly of a dipalmitoyl phosphatidyl type.¹⁵

In order to demonstrate the phospholipid layer by electron microscopy, Dermer¹⁶ used the tricomplex flocculation procedure and preserved the features of the pulmonary surfactant on the surface lining of the alveolus. In the middle ear epithelium, Lim¹⁷ demonstrated that dark granules or dark core of light granules of a subpopulation of the epithelial secretory cells were reacted with this procedure in the middle ear cavity, which showed lamellar bandings indicative of phospholipids similar to pulmonary surfactant or pure phosphatidylcholine. Mira et al¹⁸ reported the presence of osmiophilic lamellar bodies in the cytoplasm of secretory cells and of osmiophilic free lamellar membrane in the lumen of the eustachian tube glands or above the epithelium. In the present study, however, neither the secretory nor goblet cells of the middle ear were stained immunohistochemically with monoclonal antibody (PC-6 or PE-10).

The present study demonstrated the presence of an 80 kd protein in middle ear effusion, immunoreactive with monoclonal antibodies against SP-A. These antibodies stained immunohistochemically the mucosal epithelial cells of the orifice of the eustachian tube. We also suggest that this 80 kd protein might contain the structure of SP-A.

It will be interesting if this 80 kd protein is a component of a surface tension-lowering substance in the middle ear cavity that facilitates the opening of the eustachian tube. More studies are necessary for clarification.

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INTERPRETATION OF ELECTROCOCHLEOGRAPHY IN MENIERE'S DISEASE AND NORMAL SUBJECTS

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Electrocochleographic recordings were obtained from 20 subjects with normal hearing and 10 subjects with Meniere's disease by using an eardrum electrode. Stimuli included clicks and 6,000-Hz tone bursts. Results were not significantly different between the two groups for summing potential (SP) amplitude, action potential (AP) amplitude, or the SP/AP amplitude ratio. Interpreting the results in light of symptoms on the date of assessment or hearing threshold did not appear to improve separation between the two groups. Various SP/AP amplitude ratio criteria have been proposed in order to separate normal patients from those with Meniere's disease. Applying these proposed criteria to our data did not successfully separate the two groups.

KEY WORDS — electrocochleography, Meniere's disease.

INTRODUCTION

For more than a decade the ratio of the summing potential (SP) amplitude relative to the amplitude of the action potential (AP), commonly referred to as the SP/AP amplitude ratio, has been reported to be useful in the diagnosis of Meniere's disease.¹⁻⁹

Generally, it has been reported that a large SP/AP amplitude ratio indicates the presence of Meniere's disease.²⁻⁵ But interpreting the electrocochleographic findings in these patients is not always straightforward. There may be considerable variability in the results among patients with Meniere's disease. Also, the degree to which the SP/AP amplitude ratio in these patients is influenced by the amount of hearing loss or the presence of symptoms on the date of assessment is not clear. Finally, it is not certain that the diagnostic criteria for Meniere's disease were the same in all the studies or whether the study populations were indeed comparable.

The purpose of the present study was to investigate the SP/AP amplitude ratio in a group of normal subjects and in a group of subjects with a classic history of Meniere's disease and apply all of the previously recommended criteria for interpretation of the SP/AP amplitude ratio in these patients.

METHODS

The experimental group included 10 subjects with Meniere's disease, all of whom had asymmetric sensorineural hearing loss, and at least two episodes of vertigo lasting longer than 20 minutes and not longer than 24 hours that were accompanied by at

least two of the following: nausea, vomiting, change in tinnitus, exacerbation of hearing loss, or aural fullness.¹⁰ None had undergone any otologic surgery in the involved ear or had any other condition that could also cause similar symptoms. The control group comprised 20 normal subjects with hearing thresholds no greater than 15 dB hearing level (HL) from 250 Hz through 8,000 Hz in both ears and with no present or past vertigo.

Stimuli consisted of 6,000-Hz tone bursts and 100-microsecond clicks transduced through an Ety-motic insert earphone. The tone bursts had a three-cycle rise-fall time (0.5 millisecond) with a 4-millisecond plateau. A Blackman gating function was used to generate the tone burst stimuli. Stimuli were generated at rates of 11.7/s at 120 dB peak equivalent sound pressure level (peSPL) for tone bursts and 125 dB peSPL for clicks. The electrical recording was digitized for a 5.3-millisecond epoch following stimulus onset. A 2.88-millisecond prestimulus baseline was also obtained to serve as a reference in amplitude measures. Alternating polarities were used to cancel the cochlear microphonic and the stimulus artifact. Responses to 2,000 stimuli constituted each average. A replication of each average was obtained.

An advantage of the current study is that we employed a tympanic membrane (TM) electrode, which provides a larger amplitude than ear canal recordings yet is not invasive, as are transtympanic techniques. In Fig 1, comparisons of recordings using the TM electrode as compared to ear canal electrodes are provided for a normal subject. This

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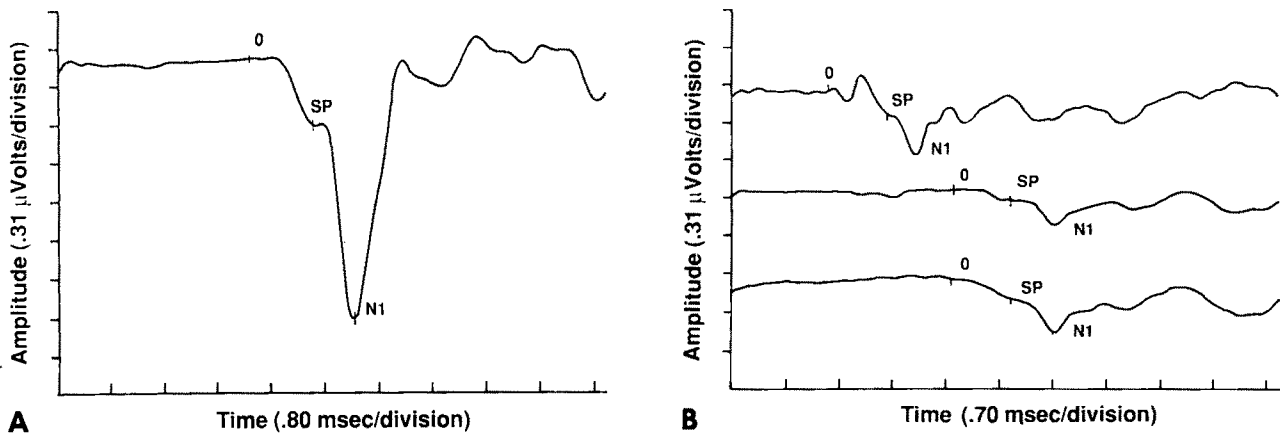


Fig 1. Electrocochleograms. SP — summing potential. A) Obtained from normal subject with tympanic membrane electrode. B) Obtained from same normal subject for same stimulus as in A but using three types of ear canal electrodes. For lower trace, 3M/Axonics reticulated foam electrode. For middle trace, Tiptrode (Nicolet) EAR plug encased in gold mesh. For upper trace, Coats or Life-Tech electrode, silver ball electrode in Mylar plastic butterfly flange. Two lower traces are delayed relative to upper trace because of 0.88-millisecond delay induced by insert earphones used with these electrodes. Note that A and B have same vertical scale. Stimulus onset is indicated by 0 for all traces.

electrode consisted of 32-gauge silver wire encased in thin (1-mm) Silastic tubing. The silver wire was hooked through a gelled foam tip approximately 3 mm wide. The hook was then retracted into the tubing, leaving only the foam tip exposed. A silver ear-clip electrode (Nicolet) was placed on the contralateral earlobe and served as the reference. A silver electroencephalic electrode was placed on the forehead and served as a ground.

Responses were filtered from 5 Hz to 3,000 Hz by employing analog filters and amplified ($\times 300,000$). Responses were then passed through a zero phase shift digital filter with a 5-Hz to 3,000-Hz band-pass. Analysis of the SP and AP recorded through similar filters has been widely reported and appears to be sufficient for clinical measurement of the SP/AP amplitude ratio.^{6,7} All testing was performed in a double-walled Industrial Acoustics Corporation sound suite.

The analysis of waveforms was carried out in the following manner. For both stimuli, the amplitude of the SP was measured from the prestimulus base-

line to the peak of the deflection (usually negative in humans) or the shoulder preceding the AP.^{1,7} Unless the knee-point of the SP preceding the AP was clearly defined, the derivative of each waveform was obtained. The AP amplitude was measured from the prestimulus baseline to the maximal peak of the N1 (Fig 2).

RESULTS

The SP amplitude was not significantly different between the normal control group and the Meniere's disease group for either the click stimuli (mean = $0.47 \mu\text{V}$, SD = 0.47 in normals; mean = $0.42 \mu\text{V}$, SD = 0.28 in Meniere's subjects) or the 6,000-Hz tone burst stimuli (mean = $0.61 \mu\text{V}$, SD = 0.51 in normals; mean = $0.43 \mu\text{V}$, SD = 0.31 in Meniere's subjects).

The amplitude of the AP was not significantly different between the two groups for either the click stimuli (mean = $1.78 \mu\text{V}$, SD = 1.34 in normals; mean = $1.43 \mu\text{V}$, SD = 0.83 in Meniere's subjects) or the 6,000-Hz tone burst stimuli (mean = $1.85 \mu\text{V}$, SD = 1.37 in normals; mean = $1.12 \mu\text{V}$, SD = 0.69 in Meniere's subjects).

The SP/AP amplitude ratio was computed for both groups. The ratio was not statistically significantly different between the two groups for either stimulus (Fig 3; click stimulus mean = 0.27 , SD = 0.15 in normals and mean = 0.31 , SD = 0.12 in Meniere's subjects; 6,000-Hz tone burst stimulus mean = 0.33 , SD = 0.12 in normals and mean = 0.40 , SD = 0.24 in Meniere's subjects). One normal subject did show a very high value, but her data were included because she met every criterion for inclusion in the normal group. She was a 21-year-old woman with no history of vertigo or otologic disorder. The recordings were clear and replicable, with an electrode impedance of $27.1 \text{ k}\Omega$.

The SP/AP amplitude ratio was more variable for the 6,000-Hz stimulus in the Meniere's disease

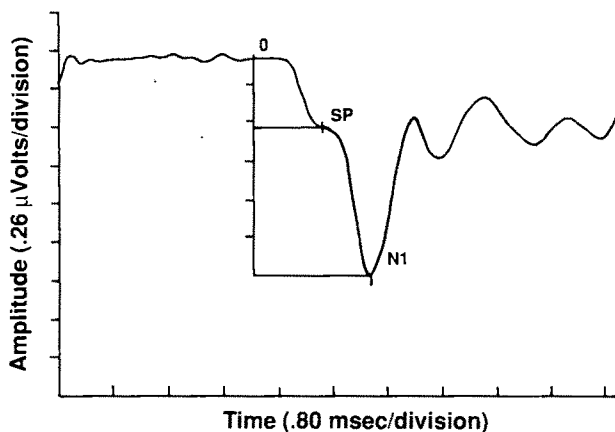


Fig 2. Method of measuring summing potential (SP) and action potential amplitude.

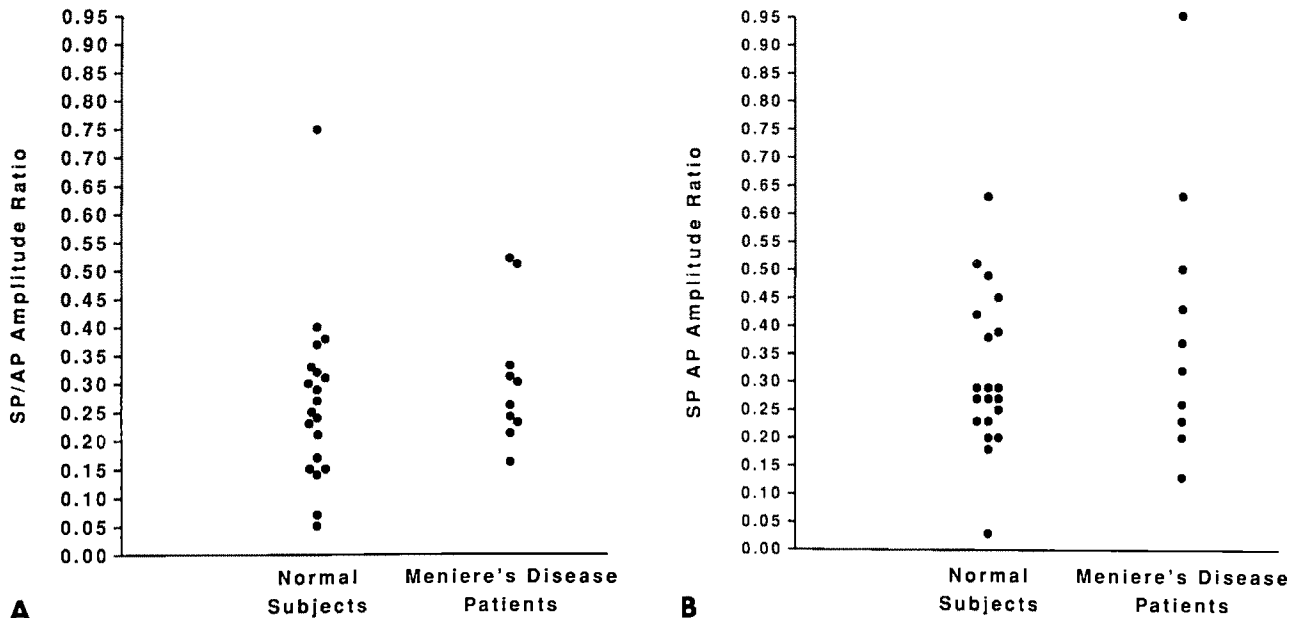


Fig 3. Scattergrams of summating potential-action potential (SP/AP) amplitude ratio for each individual patient by group. A) Click stimuli. B) 6,000-Hz stimuli.

group than in the normal control group, but no significant difference was found between groups in variability for the SP/AP amplitude ratio using the click stimulus.

DISCUSSION

The locally constructed TM electrode provided consistently clear, definable responses without requiring anesthesia or causing TM penetration. No complications resulted from use of the TM electrode.

An unexpected finding was the lack of significant difference in the SP amplitude and the SP/AP amplitude ratio between the Meniere's disease group and the normal control group. This is inconsistent with the conclusions from several previously published reports, but a closer examination of some earlier studies suggests some explanations.

Several studies report higher values for the SP amplitude and SP/AP amplitude ratio for the Meniere's disease population than for other subjects with sensorineural hearing loss,^{2,3,5,7,8,10} but studies comparing Meniere's disease subjects and normal controls are less common. Of those studies that included a normal control group, a statistical comparison of the mean SP amplitudes or SP/AP ratios was either not provided or revealed no difference.^{2,3,5,6,9} In general, the SP amplitude and the SP/AP amplitude ratio tend to be larger in the Meniere's disease subjects in the aforementioned studies as well as our own. However, a high intersubject variability in both groups precludes statistically significant differences. Using a non-Meniere's disease group with sensorineural hearing impairment as a reference possibly would have revealed larger between-group differences than using a normal control group. However, since the audiometric configurations of

patients with suspected Meniere's disease are frequently different from those of patients who clearly do not have Meniere's disease, comparisons by degree of hearing loss are difficult. In the aforementioned studies of SP amplitude and the SP/AP amplitude ratio in subjects with sensorineural hearing impairment, marked variability is evident. As early as 1979, Eggermont¹¹ suggested that the high variability of SP amplitude could preclude clinical applicability of any differences.

Rather than a comparison of the means, many authors advocated that a criterion level for the SP/AP amplitude ratio be used as a diagnostic indicator for Meniere's disease. Criterion values include 0.3,^{7,9} 0.37,⁵ 0.5,⁴ and a 95% upper confidence limit as computed from normal group data.^{2,3}

In Table 1, each of these criteria have been applied to the normal human and Meniere's disease subjects in this study. The sensitivity and specificity for each measure are included. For clinical usefulness, any test must have high values for both sensitivity and specificity. When applied to our data, none of the proposed criteria provided this.

The variability of our data appears similar to that in some other studies. The mean and standard deviation

TABLE 1. CRITERION VALUES FOR SP/AP AMPLITUDE RATIO

Criterion	Click Stimulus		6,000-Hz Stimulus	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
0.30	40	60	60	65
0.37	30	85	40	65
0.50	20	95	30	90
Above 95% confidence interval	20	95	0	95

SP — summating potential, AP — action potential.

TABLE 2. HEARING THRESHOLDS FOR MENIERE'S DISEASE SUBJECTS ON DATE OF ASSESSMENT

Subject	Hearing Threshold (dB hearing level)			SP/AP Amplitude Ratio	
	2,000 Hz	4,000 Hz	8,000 Hz	Click	6,000 Hz
1	45	55	40	0.250	0.500
2	25	40	65	0.526	0.639
3	30	20	25	0.232	0.331
4	50	50	65	0.209	0.123
5	0	20	0	0.323	0.227
6	15	20	60	0.244	0.208
7	50	35	35	0.296	0.265
8	15	30	45	0.165	0.368
9	30	20	30	0.313	0.424
10	20	20	40	0.513	0.946

SP — summating potential, AP — action potential.

ation for the click stimulus in our normal group (mean = 0.27, SD = 0.15) are similar to those reported in other studies.^{12,13} Means and standard deviations for a 6,000-Hz stimulus have not been provided elsewhere, but our values are similar to those for 2,000 Hz reported by Eggermont.⁸ The majority of studies did not report the mean and standard deviation of the SP/AP amplitude ratio for their Meniere's disease groups. As seen from the individual data points presented in those studies, the variability is obviously large.^{2,3,5,14} The values for our Meniere's disease group for click stimuli (mean = 0.31, SD = 0.12) were similar to reported values for Meniere's disease subjects with mild hearing loss. Our mean value is smaller than reported for moderate or greater hearing loss.^{7,9} Yet authors differ regarding the influence of the degree of hearing loss. Some assert that hearing loss must simply be present but with adequate residual hearing for clear recordings to observe the enlarged SP/AP amplitude ratio.⁴ Others report the degree of hearing loss to be a major influence.⁷ Still others report that hearing threshold does not markedly influence the SP/AP amplitude ratio^{2,3} or that it does not affect it for hearing loss below 50 dB HL¹¹ but does for greater losses.

Table 2 lists the high-frequency hearing thresholds for our Meniere's disease subjects on the date of assessment. All of our subjects had documented hearing loss, but because of the fluctuant nature of

the disease, one subject did not have hearing loss during the electrocochleographic measures. No consistent trend between hearing threshold and SP/AP amplitude ratio was apparent.

Ferraro et al⁴ examined the relationship of the SP/AP amplitude ratio to symptoms on the date of assessment. Symptoms examined were sensorineural hearing loss, perception of aural fullness or pressure, tinnitus, and vertigo. Vertigo and tinnitus were not found to be successful predictors of an enlarged SP/AP amplitude ratio. Whenever hearing loss and aural fullness were present together, the ratio exceeded 0.5 for click stimuli.

On Table 3, the symptoms on the date of assessment for our 10 Meniere's disease subjects are listed, as well as the SP/AP amplitude ratios. For hearing loss, we used the same criterion as Ferraro et al⁶: hearing threshold greater than 25 dB HL at any of the octave frequencies from 250 Hz to 8,000 Hz. For the 2 subjects having both aural fullness and hearing loss on the date of assessment, the SP/AP amplitude ratio was within 1 SD of the normal group and did not exceed 0.5.

Many of our Meniere's disease subjects had been under medical management for Meniere's disease prior to testing, although influence of such treatment on the SP/AP amplitude ratio is unknown. None of the previous studies reported whether or not their subjects were under any form of treatment.

A positive SP (+ SP) alone or preceding a negative SP (− SP) has been reported as indicative of Meniere's disease.^{7,14} According to these authors, the + SP component occurs most frequently in response to a high-frequency stimulus. In our data, the primary SP activity was negative for all human control subjects and Meniere's disease subjects for both stimuli. A small positive prominence did precede the − SP in 5 of 10 Meniere's disease subjects and in 15 of 20 normal control subjects for the 6,000-Hz stimulus. This prominence also appeared in 2 of 10 Meniere's disease subjects and in 6 of 20 normal subjects for the click stimulus. In these subjects, the + SP component averaged 0.04 mV —

TABLE 3. SYMPTOMS ON DATE OF ASSESSMENT OF MENIERE'S DISEASE SUBJECTS

Subject	Hearing Loss	Symptoms				SP/AP Amplitude Ratio	
		Tinnitus	Perception of Aural Fullness	Vertigo		Click	6,000 Hz
1	+	+	—	—		0.250	0.500
2	+	+	—	—		0.526	0.639
3	+	—	+	+		0.232	0.331
4	+	—	—	—		0.209	0.123
5	—	—	—	—		0.323	0.227
6	+	+	—	—		0.244	0.208
7	+	+	—	—		0.296	0.265
8	+	—	—	—		0.165	0.368
9	+	+	+	—		0.313	0.424
10	+	+	—	—		0.513	0.946

SP — summating potential, AP — action potential.

less than one tenth the size of the average - SP component. Because the incidence of a - SP component was similar in the two populations, its diagnostic significance seems limited.

Differences in electrodes and electrode placement may have caused different SP polarities to be observed. Eggermont and Odenthal,¹⁵ Kanzaki et al,¹⁴ and Gibson and Prasher⁷ used transtympanic electrodes. Mori et al¹⁶ compared transtympanic and ear canal electrode recordings. They observed the + SP only in Meniere's disease and noise-induced hearing loss, but only with the transtympanic electrodes. Comparisons with a TM electrode have recently been published by Ruth and Lambert.¹⁷ They also found the + SP component to occur less commonly with the TM recording than with a transtympanic recording site.

In summary, the SP/AP amplitude ratio did not clearly distinguish between our Meniere's disease and normal subjects. Perhaps for a certain com-

bination of hearing loss and symptoms on the date of assessment the technique could be sensitive to Meniere's disease. Many of our Meniere's disease subjects had been under medical management for Meniere's disease prior to testing, although none had ear surgery. The influence of medical treatment on the SP/AP amplitude ratio is unknown. None of the previous studies reported whether or not their subjects were under any form of treatment. All of the previous studies reported a tendency for Meniere's disease to enlarge rather than diminish the SP/AP ratio.

Nonetheless, if the SP/AP amplitude ratio cannot discriminate between 10 clear cases of Meniere's disease and 20 normal subjects, its diagnostic value in any specific patient should be viewed with caution. If this measure can only be used when a specific hearing loss or symptom is present and before any medical regimen has been employed, its applicability will be limited.

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PULL-THROUGH BRANCHIAL FISTULECTOMY: A TECHNIQUE FOR THE OTOLARYNGOLOGIST

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The complete second branchial fistula consists of a superficial infrahyoid portion and a deep parapharyngeal portion. Through the present technique, the infrahyoid portion is dissected from the neck while the parapharyngeal segment is dissected through the mouth with or without tonsillectomy. Eventually, the whole fistula is pulled out through the mouth. This technique ensures complete fistulectomy and a low recurrence rate, is more cosmetic than the traditional technique, and allows simultaneous tonsillectomy. It may not be satisfactory if the fistula was the seat of repeated infections. This technique is suitable for the otolaryngologist, who is naturally well acquainted with microsurgery and tonsillectomy.

KEY WORDS — branchial fistula, branchial system, fistulectomy.

Most complete branchial fistulae derive from the ventral portion of the second branchial cleft and the pharyngeal pouch. Typically, the external opening is in the lower third of the neck, on the line of the anterior border of the sternocleidomastoid muscle. The fistula ascends through the subcutaneous tissue, the platysma muscle, and the deep cervical fascia to reach the carotid sheath. Above the hyoid, the tract runs medially beneath the stylohyoid muscle and the posterior belly of the digastric muscle. It crosses the loop of the hypoglossal nerve and runs between the internal and external carotid arteries.¹ In the parapharyngeal space, it lies first on the middle constrictor and then on the stylopharyngeus. The fistula then crosses the latter as well as the glossopharyngeal nerve and finally pierces the middle constrictor of the pharynx.² The internal opening is in the region of the tonsillar fossa, usually on the anterior face of the upper half of the posterior pillar of the fauces¹ or in the intratonsillar cleft, which is generally held to be the site of the pharyngobranchial duct of the second pouch.³ Completeness of the fistula is diagnosed by a dye test in which methylene blue is injected through the outer opening and appears in the throat (positive test). A negative preoperative outcome on the test might become positive under anesthesia because of muscle relaxation (personal observation).

OPERATIVE TECHNIQUE

The orocervical or pull-through branchial fistulectomy is done through two portals.

Cervical Portal. Through one or two (stepped) incisions,⁴ the infrahyoid portion of the fistula is

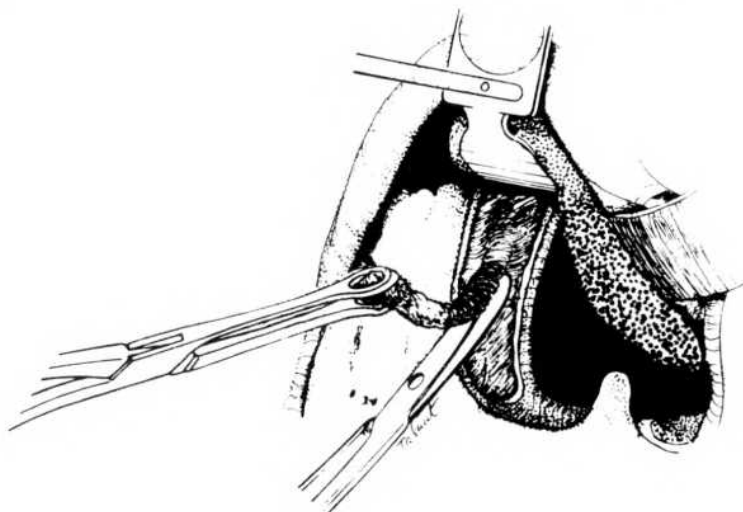
dissected. The incisions are small, just large enough to allow the introduction of a thin blunt scissors in the perifistular plane. Dissection is carried out through the lower incision upward. The fistula is delivered through the upper incision and dissection is continued upward to the hyoid bone. Then the scissors should be directed deep to dissect the lower part of the parapharyngeal portion. This type of dissection through small incisions is not dangerous if the scissors is opened in small strokes. The skin ellipse around the outer opening is cut so as not to hamper the pull-through of the fistula, and two long 1-0 silk threads are transfixed to the lower end of the fistula. These threads help in handling the fistula during dissection and will be used as drains remaining in the tunnel created after the fistula is pulled out.

Oral Portal. Using the Davis-Boyle mouth gag, the blade takes the tongue toward the unoperated side to expose the whole tonsillar fossa (see Figure). The operative dye test is done and the inner opening is identified. Usually it is in the upper half of the anterior surface of the posterior pillar of the fauces. An elliptical mucosal incision is made around the opening after infiltration with Xylocaine-Adrenalin solution. The pharyngeal end of the fistula is caught by long Allis forceps, and dissection of the parapharyngeal segment of the fistula is executed by thin, long, blunt scissors under the microscope. Sometimes the inner opening of the fistula is the mouth of the crypta magna (intratonsillar cleft). In this case, tonsillectomy is mandatory before identification of the internal opening. In either case, dissection of the upper part of the parapharyngeal segment of the fistula is continued until the hyoid bone is reached.

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Presented at the Alexandria International Conference on Pharyngeal Diseases, Alexandria, Egypt, March 22-24, 1991.

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Peroral dissection of parapharyngeal segment of complete second branchial fistula. Blade of Davis-Boyle mouth gag takes tongue toward unoperated side. In our patient, left tonsil was removed before dissection of fistula.

Gentle alternate cross orocervical traction is exerted on the fistula until its complete freedom becomes evident. The fistula is pulled out through the mouth, with the silk threads brought behind it to be used as drains for 48 hours. I do not recommend suction drainage, as this might soil the wound with septic throat contents.

The pharyngeal wound is closed by 3-0 interrupted chromic catgut sutures. The cervical wound or wounds are closed by subcuticular 4-0 nonabsorbable sutures.

DISCUSSION

Whereas dissection of the infrahyoid portion of the fistula is easy, the parapharyngeal segment needs special handling because of its deeper location and its vicinity to important neurovascular structures. The choice between two techniques managing the second branchial fistula should be based mainly on which deals better with the parapharyngeal portion. A technique is considered superior if it ensures complete excision of the fistula, is attended with minimal risk of injury to related neurovascular elements, guarantees efficient closure of the deeply seated pharyngeal mucosal defect resulting after fistulectomy, and is

more cosmetic.

In the traditional technique, the whole fistula is excised through one or two (stepped) neck incisions. The higher one should be fairly big to allow dissection of the deep parapharyngeal segment of the fistula and suturing of the still deeper pharyngeal mucosal defect resulting after fistulectomy. This, of course, should be done under vision and after identification and securing of the related neurovascular elements. In spite of camouflaging, the resultant scar in the neck is large and unsightly. Complete excision of the fistula is never sure, and closure of the deep mucosal defect in the neck is never perfect.

The present technique allows operating on the parapharyngeal segment through the mouth under the magnification and excellent lighting of the operating microscope. The internal opening is better identified and the fistula can be meticulously dissected. The pharyngeal mucosal defect is better closed from the pharyngeal side. Simultaneous tonsillectomy is possible. This technique obviates the necessity for big cervical incisions and thus is more cosmetic. The procedure is not difficult for the otolaryngologist who is capable of doing microsurgery as well as tonsillectomy.

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COMMUNICATION STATUS FOLLOWING LARYNGECTOMY: THE IOWA EXPERIENCE 1984-1987

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Data regarding treatment and outcome for a consecutive series of 73 total laryngectomy patients were collected from clinical records with a follow-up period of 30 to 78 months postoperatively. Notable findings were that 27% were women; 75% reported hoarseness or a voice change as an early symptom; and 22% reported combined heavy use of both cigarettes and alcohol. Of the 73 patients, 38 (52%) died during the follow-up period; 18 of the 38 died within 1 year postoperatively. Thirty-nine (53%) of the 73 had received a surgical tracheoesophageal fistula (TEF) for voice restoration, as either a primary or a secondary procedure. Of the 39, 75% were using the TEF at last examination, with no failures attributed to sphincter spasm. Of the total group, the primary communication modality was reported to be use of a TEF by 44% and use of an electrolarynx by 50%. Limitations of the study and directions for future investigations are discussed.

KEY WORDS — electrolarynx, laryngectomy, tracheoesophageal fistula.

INTRODUCTION

There is a continued need for information about the clinical aspects of laryngectomy and about efforts to assist patients in maintaining effective communication skills after the operation. That is especially true now with the development of the relatively new tracheoesophageal fistula (TEF) method, which is arguably the best of all methods for restoring the ability to produce sound for talking.

As indicated below, there are a number of published reports that provide partial information for this purpose, but none are so comprehensive as to be wholly satisfactory. Most notable is the need to follow a reasonable number of unselected patients through the treatment process to assist us further in understanding the variety of possible clinical outcomes from this disease and treatment strategies for it.

Ideally, information for this purpose can best be gained from a prospective design, but few working clinics are so well structured, ours included, that that is easily feasible. The obvious recourse is a retrospective endeavor, in which data are gathered as carefully as possible from available clinical records. Obviously, there are serious limitations to such a data set — mainly the probability of bias resulting from missing data. Within limits, however, the strategy seems sufficiently useful for many descriptive purposes.

There is a particular need for information about the communication skills of patients who have had laryngectomy during the last several years. Prior to the late 1970s, these patients could use a mechanical larynx (generally battery-powered), esophageal voice, or nonvoiced communication such as mouth-ing words, writing, or a communication board. The

pioneering efforts of Singer and Blom¹ and Panje² in the development of the surgical TEF with a one-way prosthesis provided an additional, highly valuable method for restoring "voice" to these patients. Several informative reports about TEF were subsequently published, among them those by Donegan et al.,³ Wetmore et al.,^{4,5} Maves and Lingeman,⁶ Stiernberg et al.,⁷ Milford et al.,⁸ Lavertu et al.,⁹ and Wenig et al.¹⁰ In addition, an impressive prospective study was reported by Blom et al.¹¹ These combined findings indicate the usefulness of the TEF procedure. However, additional findings from other treatment populations are needed to further examine the efficacy of the treatment.

Our purpose here is to report results of clinical treatment for a consecutive series of patients with laryngectomy who received surgical and speech pathology treatment in this department, with special reference to postoperative communication skills.

TREATMENT PROGRAMS

Surgery. Medical-surgical treatment for these patients was based (and is still) on the philosophy that surgical removal of the cancerous tumor, with subsequent radiotherapy if indicated, is the best option. Further, TEF is considered for every patient: as a component of the laryngectomy (primary TEF) if no subsequent irradiation is planned, and later (secondary TEF) if irradiation is planned.

The surgical procedure has been described previously.⁶ A laryngectomy or laryngopharyngectomy is first accomplished with attention to wide margins and standard oncologic technique. The tracheostome is created. An incision is made in the posterior membranous wall of the trachea so that a hemo-

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stat may be directed into this wound through the esophageal lumen. A 10F to 14F flexible catheter is then directed inferiorly into the stomach, ascertained to be in position, and secured in place. The incision for the TEF is made about 1 cm below the anticipated mucocutaneous verge of the tracheostome. If sufficient pharyngeal tissue remains, then a standard closure of the pharynx is accomplished. An important feature of the procedure is that the pharyngeal musculature is not fully joined, providing perhaps the same effect as a later myotomy. On the other hand, some patients require augmentation of this pharyngeal tissue; in these cases a myocutaneous flap is incorporated into the closure to provide sufficient augmentation to the pharynx so that it can be easily closed over a No. 36 bougie. The suggested method of closing a small remnant of pharyngeal mucosa over a nasogastric tube, with the provision that it may be dilated later, is not followed.

Postoperatively, the patient's nutrition is maintained through this tube into the tracheoesophageal fistula. Oral alimentation occurs at the normal 10- to 14-day postoperative interval, and at the same time, attempts at early phonation may be begun under the supervision of a speech pathologist. Either the Blom-Singer or the Panje prosthesis is used, depending on the configuration of structures and functional results. The choice of prosthesis is made cooperatively by the surgeon, speech pathologist, and patient. Frequently, both types are tried on an experimental basis before a final decision is made. Clinical observations indicate that the Blom-Singer prosthesis requires less air pressure for phonation. The variety of lengths of the Blom-Singer prosthesis is also advantageous. Easy commercial access and lower cost are also factors. On the other hand, the Panje prosthesis is very useful for the patient whose TEF is not near the margin of the stoma or who cannot tolerate the adhesive tape needed to secure the tab of the Blom-Singer prosthesis near the edge of the stoma. There may also be differences in choice of prosthesis according to the construction of the fistula (so-called surgical slant).

When secondary TEF is performed, the procedure described by Panje² is followed on an outpatient basis. The choice of prosthesis is based on the considerations previously described.

Speech Pathology Services. Patients scheduled to have laryngectomy are routinely examined and counseled by a speech pathologist before the operation. The purpose of the interview is to discuss general effects of the operation on oral communication, to review briefly the treatment plan for assisting in the maintenance of oral communication, to introduce speech pathology personnel, to identify psychological and social characteristics of the patient and the family that may be relevant to treatment, and to answer questions. There is considerable variation among patients in the amount of technical de-

tail provided, depending on the emotional status and background of the patient.

We consider TEF to be the method of choice for oral communication for these patients and use it for all patients unless there are clear contraindications. However, since several months may intervene between the laryngectomy and the functional TEF voice, we dispense an electrolarynx to each patient whom we judge capable of using it. Usually, the device is dispensed and instruction and practice for its use are provided before hospital discharge. Sometimes we refer the patient for therapy in use of the electrolarynx in the home community. Oral speaking tube adaptations of the electrolarynx are needed for some patients, although in general we find them unsatisfactory. Patients who cannot use an electrolarynx usually communicate by writing or are provided a communication board. In all cases, family counseling and training are available to aid in understanding the patient's status and attempts to cope with the situation.

As indicated earlier, at our institution (along with most others in the United States), surgery is considered the best initial treatment for laryngeal cancer, followed by radiotherapy if indicated by the finding of positive neck nodes or an extensive primary lesion. Since irradiation of the neck region commonly results in tissue changes (such as swelling and stiffness) that are not conducive to learning TEF voice, the decision between primary and secondary TEF is based on whether postoperative radiotherapy is planned.

This practice is in contrast to the typical European one, in which radiotherapy is administered as the preferred treatment mode, followed by surgery if indicated. In that philosophy, it seems likely that a higher percentage of TEF procedures would be performed on a primary basis.

Our goal for patients with primary TEF is production of sound within 2 weeks, usually before the patient is discharged or soon thereafter. Results are more quickly obtained when the TEF is a secondary procedure, since the patient is then in better health. The secondary TEF procedure is performed on an outpatient basis. In either a primary or secondary TEF, a Foley catheter is inserted into the fistula to prevent aspiration until placement of the prosthesis. The patient can withdraw the catheter for short periods of time to practice phonation. The patient returns 10 days later for evaluation of healing and assistance with phonation.

In the case of either primary or secondary TEF, the speech pathologist instructs the patient about insertion, removal, and care of the catheter — and later the prosthesis — and about practicing phonation. On occasion, the patient is referred to a speech pathologist in the local community for assistance with the TEF voice. Esophageal insufflation before

TABLE 1. DESCRIPTION OF 73 PATIENTS

	No. of Pts	%
Race		
White	70	96
Black	3	4
Sex		
Male	53	73
Female	20	27
Age at operation (range 28-87 y)		
≤ 50	8	11
51-60	19	26
61-70	29	40
71-80	14	19
≥ 81	3	4
Carcinoma type		
Squamous cell	71	97
Chondrosarcoma	1	1
Spindle cell	1	1
Staging ^{12,13}		
I	3	4
II	7	10
III	26	36
IV	33	45
Not relevant	2	3
Not recorded	2	3
Procedures		
Laryngectomy only	10	14
Laryngectomy with neck dissection and/or thyroid lobectomy	33	45
Laryngectomy with neck dissection and/or glossectomy and/or other	30	41
Glossectomy 11/30		
Jejunal graft reconstruction 3/30		
Tracheoesophageal fistula		
Primary*	30	41
Secondary	9	12
Length of hospitalization (d)		
1-10†	3	4
11-20	42	58
21-30	18	25
31-40	4	5
41-50	3	4
≥ 51	3	4
Other medical therapy		
Radiotherapy§	39	53
Elsewhere 9/39		
Recommended but not taken	2	3
Chemotherapy	2	3

*Patients without irradiation planned for after laryngectomy.

†Two patients transferred to Veterans Administration Medical Center.

§After laryngectomy in 38/39 cases.

creation of the TEF has not proved useful in predicting success of the TEF voice and is not performed. Myotomy of the pharyngeal constrictor is considered useful only rarely.

Both the Blom-Singer and Panje prostheses are available for use; the choice between them depends on the site of the fistula and the obtained result. Observation and treatment are continued on a periodic basis as needed.

METHODS

Clinical records (the hospital chart and speech

pathology records) were reviewed for all patients who were coded by the Medical Records Department of The University of Iowa Hospitals and Clinics as having laryngectomy in this hospital during the calendar years 1984 through 1987. The criterion for inclusion in this study was that total laryngectomy was performed. (Those with partial laryngectomy were excluded.) The clinical records were examined to confirm the suitability of each patient and for the collection of the following data: age, gender, race, tumor stage, operation performed (relevant to the laryngectomy), medical history, medical and speech pathology treatment and follow-up, and current status.

The majority of surgery and postoperative care was provided by author M.D.M. or under his supervision. The majority of speech pathology care was provided by author D.R.V. or under his supervision. All data were taken by the two senior authors (H.L.M. and A.E.S.), working independently after training together in data collection from the records of the first 12 patients.

RESULTS

Surgical Treatment. During this 48-month period, 73 patients met the criterion of total laryngectomy in this department. As indicated in Table 1,^{12,13} the majority were white men who were operated on after the age of 60. All but 2 had squamous cell carcinoma.

The TNM staging was performed clinically according to guidelines recommended by the American Joint Committee on Cancer.¹² We followed the suggestions by Sessions¹³ for stage grouping; 59 (86%) of the 69 patients with staging had stages III and IV.

Only 10 (14%) had simple laryngectomy; 30 (41%) had multiple procedures, including 11 patients with glossectomy (partial or total) and 3 with jejunal graft reconstruction. The operations for 30 of the 73 included construction of a TEF. Four of the 30 primary TEF patients had subsequent reoperation of the TEF because of narrowing of the initial surgical fistula. An additional 9 had TEF later as a secondary procedure. Hospitalization for laryngectomy ranged from 10 to 90 days, with that for 60 of the 73 (83%) between 11 and 31 days.

Just over half (39) had radiotherapy, typically 60 Gy over 6 weeks; 38 of the 39 patients had the radiotherapy immediately after laryngectomy. Only 2 had chemotherapy.

As indicated above, the clinical criterion for performing primary TEF was that radiotherapy was not planned immediately following the laryngectomy. The findings indicate that that criterion was frequently not observed. Of the 30 patients with primary TEF, 15 (50%) did indeed have radiotherapy immediately after laryngectomy; and of the 9 patients with secondary TEF, 3 did not.

TABLE 2. SYMPTOMS AND MEDICAL HISTORY OF 73 PATIENTS

	No. of Pts	%
Initial complaints (not mutually exclusive)		
Hoarseness or voice changes	55	75
Swallowing problems	41	56
Sore throat	31	42
Weight loss	30	41
Cough	18	25
Other: stridor or wheezing, neck nodes, ear pain, shortness of breath, blood in sputum, etc		
Medical history of previous cancer (not mutually exclusive)		
Previous laryngeal or oral cancer diagnosis	28	38
Previous laryngeal or oral cancer surgery (including laser)	14	19
Previous radiotherapy for laryngeal or oral cancer	28	38
Previous other cancer	4	5
Family history of cancer (all types and sites)	9	12
Medical history of other health problems (not mutually exclusive)		
Hypertension	6	8
Diabetes	5	7
Cardiac	5	7
Head and neck trauma	4	5
Neurologic or psychiatric	5	7
Cerebrovascular	2	3
Miscellaneous, minor	35	48

Medical History. Predominant presenting symptoms (Table 2) were hoarseness or other voice changes (75%), dysphagia (56%), sore throat (42%), and weight loss (41%). One third (38%) had previous treatment of some kind for laryngeal or oral cancer (Table 2). Forty-four (60%) had additional health problems.

History of tobacco and alcohol use is reported in Table 3. One in three patients reported cigarette pack years exceeding 61; 16% reported pack years exceeding 91. Heavy alcohol use or recognized alcoholism was reported by 45%. Nearly one in four gave a history of heavy tobacco use (70 pack years or more) in combination with heavy alcohol use.

Surgical Follow-up. As shown in Table 4, fistulas

TABLE 3. REPORTED HISTORY OF TOBACCO AND ALCOHOL USE IN 73 PATIENTS

	No. of Pts	%
Cigarette smoking (pack years)		
None	3	4
1-20	5	7
21-60	31	42
61-90	13	18
≥ 91	12	16
Not reported	9	12
Alcohol use		
None	10	14
Social light	12	16
Moderate	4	5
Heavy or alcoholic	33	45
Not reported	14	19
Combination of ≥ 70 pack years plus heavy or alcoholic use	16	22

TABLE 4. MEDICAL COMPLICATIONS IN AND FOLLOW-UP OF 73 PATIENTS

	No. of Pts	%
Complications during recovery		
Fistula formation (5/15 had primary tracheo-esophageal fistula)	15	21
Other: esophageal stenosis, bronchospasm, neck abscess, infection, pneumonia, etc	22	30
Medical and surgical follow-up		
None, referred elsewhere for follow-up	7	10
Never discharged	2	3
None, never returned	2	3
At least one return	62	85
No. of returns		
1-5	21	34
6-10	13	21
≥ 10	28	45

developed postoperatively in 15 patients (21%), a higher frequency than the 15% reported by Arriaga et al.¹⁴ Five of the 15 patients who developed postoperative fistulas had TEF concurrent with the laryngectomy operation. Other complications were reported for 30% of the 73 patients. Medical and surgical follow-up was completed for the majority of patients; of those returning for follow-up care, 66% returned for more than six visits.

Current status was assessed June 30, 1990; the postoperative period ranged from 30 to 78 months. At that assessment (Table 5), 33 patients (45%) were living; 38 (52%) had died; and status could not be determined for the remaining 2. Of those living, all were more than 24 months postoperative and 15 were more than 61 months postoperative.

Eighteen (47%) of the 38 who died did so during the first postoperative year. The cause of death was reported for 30 of the 38; of that number, cancer was listed as the primary cause for half. Table 5 gives survival data for the 10 patients with simple laryngectomy; 60% survived, as compared to 45% for all 73 patients.

Speech Pathology Follow-up. Thirty of the 73 pa-

TABLE 5. CURRENT STATUS (JUNE 30, 1990, 30 TO 78 MONTHS POSTLARYNGECTOMY) FOR ALL 73 PATIENTS AND FOR 10 WITH SIMPLE LARYNGECTOMY

	All 73		10 Simple	
	No.	%	No.	%
Living (last report; mo postoperatively)	33	45	6	60
0-12	0	0	0	0
25-60	18	55	6	100
≥ 61	15	45	0	0
Deceased (mo postoperatively)	38	52	4	30
0-12	18	47	2	50
13-24	6	16	1	25
25-36	8	21	1	25
37-48	6	16	0	0
Status unknown	2	3	0	0
Cause of death in 38 deceased: cancer 19, cerebrovascular accident 2, cardiac arrest 4, septic shock 5, unknown 8.				

TABLE 6. SPEECH PATHOLOGY FOLLOW-UP IN 73 PATIENTS

	No. of Pts	%
Preoperative examination		
Yes	43	59
No	30	41
No. of in-house visits for treatment		
None	3	4
1-6	33	45
≥ 7	37	51
No. of postdischarge visits		
None	21*	28
1-3	23	32
4-6	17	23
≥ 7	12	16

*Medical referral elsewhere 7; no medical return 2; too ill 3; reason not apparent 9.

tients had laryngectomy before their first examination by the speech pathologist (Table 6), but in-house consultation and postoperative treatment were provided to nearly all (70 of 73). Follow-up after discharge was poorer for speech pathology than for medical and surgical care, with 21 patients (29%) never seen after discharge.

As indicated earlier, 30 of the 73 patients had primary TEF (Table 7). Follow-up was not possible for 7. Of the remaining 23, at the last examination, the TEF was in use with various degrees of success for 17 (74%), and had been terminated for 6 (26%).

Nine patients had secondary TEF, the majority within 1 year after laryngectomy (Table 7). Follow-up was possible for eight of the nine; of the eight, the TEF was in use at last examination for six (75%), and had been terminated for two (25%). One patient with secondary TEF had a myotomy performed 6 months after TEF; myotomy was recommended but not performed for another secondary TEF patient. Both were using TEF voice (with easy conversational proficiency) at last examination.

As shown in Table 8, 26 (50%) of the 52 patients with speech pathology follow-up were using an electrolarynx as the primary mode of oral communication at last examination, and 23 (44%) were using TEF voice. The Romet was the most frequently used electrolarynx, followed by the Western Electric and then the Cooper Rand; nearly half of these patients used several types before selecting one. There was a nearly equal division among the TEF users between the Blom-Singer and the Panje prostheses; about one third of the total group had used both prostheses before selecting one. Twelve of the 52 patients with speech pathology follow-up used both TEF and an electrolarynx. One patient was using esophageal voice, and 2 were not speaking.

Clinical ratings of voice proficiency are routinely made for all laryngectomy patients who use an electrolarynx, TEF, or esophageal voice. A five-point scale is used, ranging from 1 (minimal sound) to 5

TABLE 7. FOLLOW-UP FOR PATIENTS WITH TRACHEOESOPHAGEAL FISTULA

	No. of Pts	%
Primary (30 patients)		
No follow-up (early death)	6	20
No follow-up (moved)	1	3
With follow-up	23	77
Fistula in use	17	74
Use of fistula terminated	6*	26
Secondary (9 patients)		
Timing after laryngectomy (mo)		
0-6	4	44
7-12	4	44
≥ 13	1	12
No follow-up (moved)	1	12
With follow-up	8	88
Fistula in use	6	75
Use of fistula terminated	2†	25

*Chronic aspiration, arthritis, or other health problems in 3; lack of motivation, anxiety, or failure to practice in 3.

†Chronic aspiration, arthritis, or other health problems in 1; lack of motivation, anxiety, or failure to practice in 1.

(superior skill). These ratings for the 26 electrolarynx patients and the 23 TEF patients, at time of the last examination, are shown in Table 8. The ratings indicate a range of proficiency for both groups, with somewhat more electrolarynx users demonstrating high proficiency than TEF users.

Apparent reasons for TEF failures are reported in Table 7 (footnotes) and are evenly divided between medical and behavioral factors. No failures were judged to be related to esophageal spasm requiring myotomy.

There is a general supposition that a patient who receives radiotherapy immediately after laryngectomy is a poorer TEF candidate than one who does not. In this series, that supposition is not supported. As stated above, 15 of the 30 primary TEF patients subsequently had radiotherapy. Of the 15, the TEF was functioning at time of last examination for 9; there was TEF failure in 1 patient; and there was no follow-up because of death in the remaining 5. Comparable numbers for the 6 patients who had

TABLE 8. SPEECH PROFICIENCY RATINGS AT LAST EXAMINATION FOR 52 PATIENTS WITH SPEECH PATHOLOGY FOLLOW-UP

Rating	No. of Patients			
	Electrolarynx	Primary TEF	Secondary TEF	Total TEF
1 (minimal sound, not volitional)	0	2	0	2
2 (limited conversational)	5	3	3	6
3 (easy conversational)	5	5	3	8
4 (fluent, comfortable)	8	4	0	4
5 (superior skill)	6	3	0	3
Not reported	2			
Total	26	17	6	23

One patient used esophageal voice, and two patients were nonspeaking.
TEF — tracheoesophageal fistula.

TABLE 9. COMPARISON OF RESULTS WITH TRACHEOESOPHAGEAL FISTULA ACROSS STUDIES

Type of Fistula	Study	No. of Pts	Type of Prosthesis	Length of Follow-up	Rate of Success
Primary	Stiernberg et al ⁷	20	Bivona	7-24 mo	60% fluent speech
	Milford et al ⁸	36	Blom-Singer	4-48 mo	89% fluent speech
	Wenig et al ¹⁰	19	Blom-Singer	NR	58% functional use
	Morris et al	30	Blom-Singer	30-78 mo	71% easy conversation or better
Secondary	Donegan et al ³	23	Blom-Singer	NR	57% intelligible and can maintain prosthesis
	Wetmore et al ⁵	66	Blom-Singer	1-3 y	64% functional use
	Wenig et al ¹⁰	18	Blom-Singer	NR	44% functional use
	Lavertu et al ⁹	111	Mueller	6 mo	59% good or excellent skills
	Morris et al	9	Blom-Singer	30-78 mo	50% easy conversation or better

NR — not reported.

secondary TEF after radiotherapy following laryngectomy were 3 with a functioning TEF, 2 failures, and 1 with no follow-up because of moving.

Data for comparison to other reported TEF results are presented in Table 9^{3,5,7-10}; number of subjects, prosthesis used, follow-up period, success rate, and criterion for success. The evaluation methods used in these seven studies are sufficiently similar that results can be compared with some confidence. Less clear from the reports is whether each sample was taken without regard to extraneous selection factors that might bias the results. To our knowledge, ours is a consecutive series.

Success rates for primary TEF range from 58% and 60% to 89%. Success rates were lower for secondary TEF, with only Wetmore et al⁵ reporting results that approximate a 64% rate. We regard our data on secondary TEF as preliminary, since our sample is so small.

Surgical Subgroups. It might be supposed that the 10 patients who had simple laryngectomy had less extensive disease and responded well to treatment. Examination of our findings for them indicates that is not necessarily the case. Half of the 10 had tumors staged III or IV. Six (60%) of the 10 survived this period of study, in contrast to 45% of the total group. The 4 who died did so within 2 years of operation. Seven had TEF (4 primary); of the 7, the TEF had been terminated in 4. Nine of the 10 were using an electrolarynx at time of last examination.

Finally, we present data for two other surgical groups, since they are of special interest. The jejunal graft reconstruction is usually regarded as a radical treatment strategy, and not much follow-up information is available about patients who have had it. We report three patients here, but follow-up data on only two, since the third was transferred. One died 2 years postoperatively, and had been using an electrolarynx with ease (rating of 3). The other was living 6 years postoperatively, with fluent use of the electrolarynx (rating of 4).

The 11 patients who had glossectomy are of special interest to the speech pathologist, since the tongue is so vital to speech production, and struc-

tural or motor impairment is so difficult to compensate for. The 6 patients who had total glossectomy died within 1 year of operation (5) or were lost to follow-up (1). Three of the 5 with partial glossectomy died. The remaining 2 are living, and apparently demonstrating moderately successful oral communication skills. (One used a secondary TEF with a rating of 2, and the other used an electrolarynx with a rating of 3.)

DISCUSSION

The obtained findings from this consecutive series on laryngeal cancer and its treatment are relatively consistent with general expectations and previous reports. This is a serious, life-threatening disease that afflicts more men than women, mostly after the sixth decade of life. Most commonly, the size and location of the malignancy requires extensive surgery and, frequently, radiotherapy. Only 2 of these 73 patients had chemotherapy. For the majority, hospitalization following laryngectomy did not extend past 2 to 3 weeks; however, medical and surgical complications, including those requiring longer hospitalization, were not uncommon.

Slightly more than half (52%) of the 73 patients died during the follow-up period (30 to 78 months postlaryngectomy) — more during the first year than in any year following. Of the 38 who died, cancer recurrence was known to be the cause of death in half, and a probable contributor although unreported in more. A somewhat higher survival rate (60%) was observed for the 10 patients who had simple laryngectomy.

Three of the early symptoms or initial complaints of laryngeal cancer are likely to be recognized by the public as health problems for which to seek medical assistance: swallowing problems, sore throat, and weight loss. The fourth symptom, and most commonly reported (75%) — hoarseness or change in voice quality — merits special comment here. Since changes in vocal quality may not ordinarily be interpreted by the public as an important clinical signal, we need to increase our efforts at public education. On the basis of current information, we need to tell the public often that in the absence of an upper respiratory tract infection or allergy, hoarseness or a change in voice in anyone old-

er than 50, for more than 2 weeks, should be regarded with proper concern and should be investigated by an otolaryngologist.

The laryngectomy operation followed other treatment for laryngeal or oral cancer in a substantial number of the patients. However, in all but four, the laryngeal or oral cancer was reported to be the primary lesion.

Our findings also substantiate the general finding that frequent cigarette smoking and alcohol use are risk factors in laryngeal cancer, particularly in interaction¹⁵: 22% of the 73 patients reported 70 pack years or more together with heavy alcohol use or alcoholism.

One difference from other published reports is the relatively high percentage (27%) of women in the sample. Romm¹⁶⁽¹⁰⁹⁾ suggests that laryngeal cancer is "10 times more common in men than in women." McGuirt¹⁷ reported that 16% of his sample of 170 patients with laryngeal cancer were women. Our findings are highly similar to those reported by Lavertu et al⁹: 30 (26%) of their 117 patients were women.

McGuirt attributes a probable increase of laryngeal cancer in women to an increase in tobacco use. Our sample of 20 women was highly similar to the entire study group of 73 in regard to history of heavy cigarette smoking (30% had 61 pack years or more); alcohol abuse (35% had heavy or alcoholic use); combined cigarette and alcohol use (20%); and percentage of deaths (50%). Thus, the clinical picture for these women with laryngeal cancer is very much the same as for the series.

The findings indicate that all but 2 of the 52 patients with speech pathology follow-up had a functional oral communication strategy. Division between TEF and the electrolarynx was nearly equal. One patient was using esophageal voice.

The success rates for both primary and secondary TEF seem comparable to those reported by other treatment centers — especially notable because this was a consecutive series of nonselected patients. Reasons for failure of the TEF strategy were divided evenly between physiologic and behavioral factors. The physiologic factors included chronic aspiration and other health problems such as arthritis.

A striking difference between these findings and those reported by other investigators is in the need for myotomy in treatment for unsuccessful TEF. Singer et al^{18,19} have considered pharyngoesophageal spasm to be a major factor in TEF failure and have advocated the use of myotomy in selected patients for spasm relief. The rationale and procedure for myotomy have been described also by Henley and Souliere²⁰ and Mahieu et al.²¹ Wenig et al¹⁰ report performing myotomy of the pharyngoesophageal segment routinely with laryngectomy. Only 1

of the 39 TEF patients in our series had a myotomy; the recommendation was made for another patient but not implemented. Both were using TEF voice satisfactorily at last examination. Two possible explanations are considered likely for this difference. One is the method of pharyngotomy closure: a firm closure of the esophageal muscles during the laryngectomy is avoided, decreasing the probability of a subsequently tight esophageal sphincter. This probability is alluded to also by Shagets and Panje.²² More data are needed about these relationships.

Another possibility is our practice of delaying insertion of the prosthesis until phonation is easy to perform and of satisfying quality. There is also the added benefit that most patients and families seem to find the catheter easy to insert into the fistula and more easily manageable in general than the prosthesis in the early postoperative weeks. The extended use of the catheter and the delay in placing the prosthesis appear to be generally beneficial.

That the electrolarynx is used as the primary mode of oral communication by half of the patients was a considerable surprise to us. The highest usage rate reported that we know about was 35% of 47 patients with 6-month follow-up.²³ We wonder whether we have been sufficiently aggressive in exploring the possibility of the TEF with those who have not had it, and in assisting those who have had experience with it to use it satisfactorily. Perhaps the finding reflects characteristics of our population, such as advanced age or rural settings in which therapy services are not easily available, but that seems unlikely.

This study is not useful in evaluating relative effectiveness of the Blom-Singer and Panje prostheses, since the data do not permit comparison. In our experience both are useful in different patients for different reasons, and both should be considered in clinical planning.

We continue to regard the TEF procedure as the very best method for restoring the ability to orally communicate to the laryngectomy patient. Certainly it is far easier to administer than is instruction for esophageal voice in the majority of these patients, and hence less costly in resource use. However, as is evident from these findings, many patients find the electrolarynx to have an equal or greater advantage.

Two comments about updates in clinical practice are warranted. One is that author M.D.M. now uses a silicone rubber tube to occlude the fistula (before placement of the prosthesis) in preference to a red rubber catheter. Red rubber appears to cause a fair amount of granulation tissue about the fistula site, which can be troublesome. The silicone catheter can be devised from a Jackson-Pratt drain tube, or is available commercially. The second is that author D.R.V. now uses the Romet electrolarynx in

preference to all other types because of the high quality of results.

Finally, the limitations inherent to an investigation of this kind must be acknowledged. The validity of data gathered retrospectively from clinical records rests on the presumption that the clinical material was obtained and recorded in a consistent manner. Experienced clinicians will freely admit

that is not always the case. Our focus here was primarily on issues of treatment and outcome that are sufficiently important to clinical management of the patient that the data about them were likely to be well recorded. In our opinion, if there are aspects of the obtained data that are misleading, they would be the results of underreporting, and not apt to lead to wrong conclusions that are damaging to our purpose.

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RAPID VOICE TREMOR, OR "FLUTTER," IN AMYOTROPHIC LATERAL SCLEROSIS

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In an attempt to clarify the origin and frequency characteristics of a rapid voice tremor, or "flutter," in patients with amyotrophic lateral sclerosis (ALS), eight patients (four men and four women; ages 42 to 70 years) who had ALS and rapid voice tremor and an age- and sex-matched control group of eight subjects were asked to sustain the vowel /a/ and their voices were recorded for later analysis. Each segment of phonation was demodulated into amplitude and frequency components. From each subject's 8-second amplitude and frequency signals, a fast Fourier transform analysis was done on a 1-second segment previously identified perceptually as having the most apparent tremor or flutter. The results showed that patients with ALS had multiple combinations of levels and frequencies for amplitude and frequency modulations in comparison with control subjects, who had consistently low levels of modulations. In an attempt to quantify the tremor or flutter in ALS, amplitude and frequency modulations were not clearly or predominantly represented at one point along the spectrum. Nevertheless, these frequency and amplitude modulations are more prominent in patients with ALS than in normal subjects. The origins of these aberrant frequency and amplitude modulations in ALS patients remain obscure, although speculation is that they are of peripheral rather than central nervous system origin.

KEY WORDS — amplitude and frequency modulations, amyotrophic lateral sclerosis, flutter, tremor.

Tremor is pervasive in neurologic disease. It also occurs in a normal nervous system. There is no uniform definition or classification of tremor, but students of the phenomenon agree that it is an involuntary, periodic oscillation of a body member, continuous and rhythmic in appearance and distinguishable from other involuntary movements. The frequency, waveform, and amplitude of tremor are known

to be determined by the underlying pathophysiologic mechanism causing it.¹

Normal individuals produce a physiologic tremor within a frequency range of 6 to 12 Hz.^{2,3} Abnormal tremors in neurologic disease can be classified by frequency band. In the band from 1.5 to 3 Hz are found the coarse tremors in cerebellar ataxia involv-

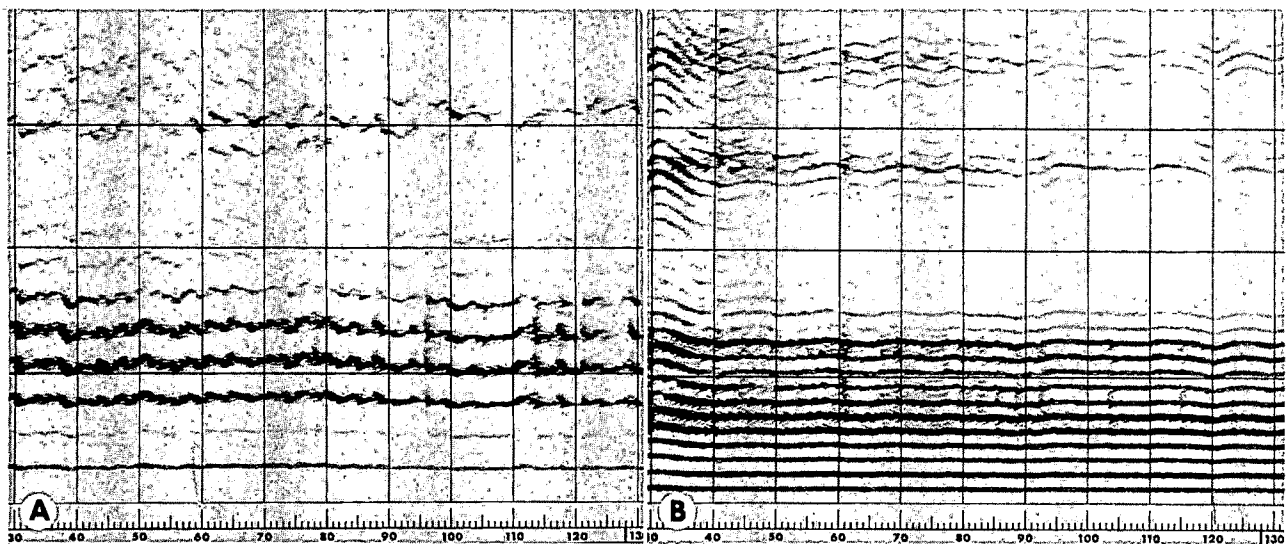


Fig 1. Sonograms of vowel prolongation. A) In patient with amyotrophic lateral sclerosis. B) In control subject.

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TABLE 1. CLINICAL DATA FOR EIGHT PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS WHO HAD RAPID VOICE TREMOR

Subject	Sex	Age (y-mo)			Bulbar Signs Only	Bulbar and Spinal Signs	Phonatory Defects				Articulation Defect
		At Exam	At Onset of General Symptoms	At Onset of Speech Symptoms			Strained-Hoarse	Breathy	Wet-Hoarse	Hypernasal	
1	F	68-6	64-11	68-0	-	+	+	-	-	+	+
3	F	67-4	66-2	65-11*	-	+	+	+	-	+	+
5	M	54-0	54-1	54-6*	+	-	+	-	-	-	-
7	M	63-9	62-3	62-5	-	+	-	-	+	+	+
9	M	51-10	49-10	51-4	-	+	-	+	-	+	-
11	F	69-8	69-4	68-10*	-	+	+	-	+	+	+
13	F	55-10	55-2	54-11*	-	+	+	-	-	-	+
15	M	41-9	61-3	41-1*	+	-	+	-	-	+	+

All patients had tongue fasciculations, and all except patient 1 had mixed (flaccid-spastic) dysarthria.

*Speech changes preceded other neurologic signs in these patients.

ing the head, trunk, and upper extremities. In the band from 4 to 6 Hz are the tremors that occur in parkinsonism. Patients who have Parkinson's disease produce voice tremor calculated to occur within the range of 4 to 7 Hz.⁴

Essential tremor of the limbs ranges from 4 to 9 Hz, and that of the head is about 4 Hz.¹ Organic voice tremor, a laryngeal form of essential tremor, can become so severe that during the adductor phase of the vocal fold tremor complete voice arrests can occur, producing a form of adductor spastic (spasmodic) dysphonia.⁵

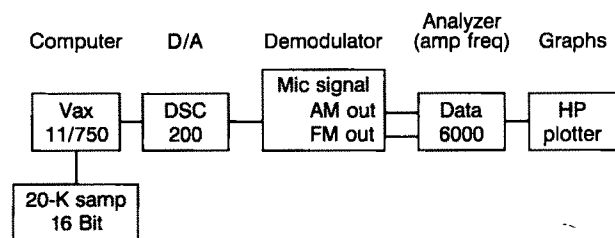
Tremors in the band from 8 to 12 Hz, the highest found in humans, are interpreted as exaggerations of physiologic tremor and are most commonly associated with anxiety. However, high-frequency tremors also occur in central nervous system degenerative diseases and multifocal infarcts, in peripheral neuropathy in which there are individual violent muscle twitches, and in many states of drug intoxication.¹

Typically, the bulbar form of amyotrophic lateral sclerosis (ALS) produces a flaccid dysarthria, a spastic dysarthria, or both, depending on the stage of the disease. In fully developed flaccid-spastic dysarthria,

the patient's phonation has a strained, wet hoarseness, resonance is hypernasal, and articulation is slow and imprecise.⁶ The physical signs that underlie the dysarthria consist of unilateral or bilateral flaccid weakness of one or both true vocal folds; spastic hyperadduction of the false vocal folds; unilateral or bilateral weakness of the soft palate; weakness, atrophy, and fasciculations of the tongue; and weakness of the lips.

Subsequently, Aronson⁷ added a further clinical observation to these already established dysarthric signs in ALS by noting that on vowel prolongation many ALS patients had a rapid voice tremor, or "flutter," that was almost undetectable during conversational speech. This tremor and its frequency and amplitude had not been reported previously, and a physiologic explanation for its presence is yet to be established. Acoustic spectrographic recordings of patients with ALS who have rapid tremor or flutter produce sonograms with an obvious disturbance in vowel/a/ prolongation (Fig 1A) when compared with recordings of a normal subject (Fig 1B). To the ear, the flutter is rhythmic, but its complexity and lack of demarcation among fluctuations on the sonogram prevent visual quantification.

This study was done to quantify the frequency of perceptual flutter in patients with ALS by means of a fast Fourier transform (FFT) analysis. Knowledge of



Data file

Fig 2. Block diagram of instrumentation for analysis of acoustic data. D/A — digital to analog, DSC — Digital Sound Corporation, HP — Hewlett-Packard, Mic — microphone, samp — sampling rate, Vax — computer.

TABLE 2. PEARSON PRODUCT-MOMENT CORRELATION COEFFICIENTS

	Patient Data	Control Data
Amplitude spectral peaks (Hz)	0.87	0.97
Amplitude spectral peaks (mV)	0.99	0.99
Frequency spectral peaks (Hz)	1.00	0.80
Frequency spectral peaks (mV)	0.99	0.91

For repeated measurements of fast Fourier transforms from demodulated amplitude and frequency data.

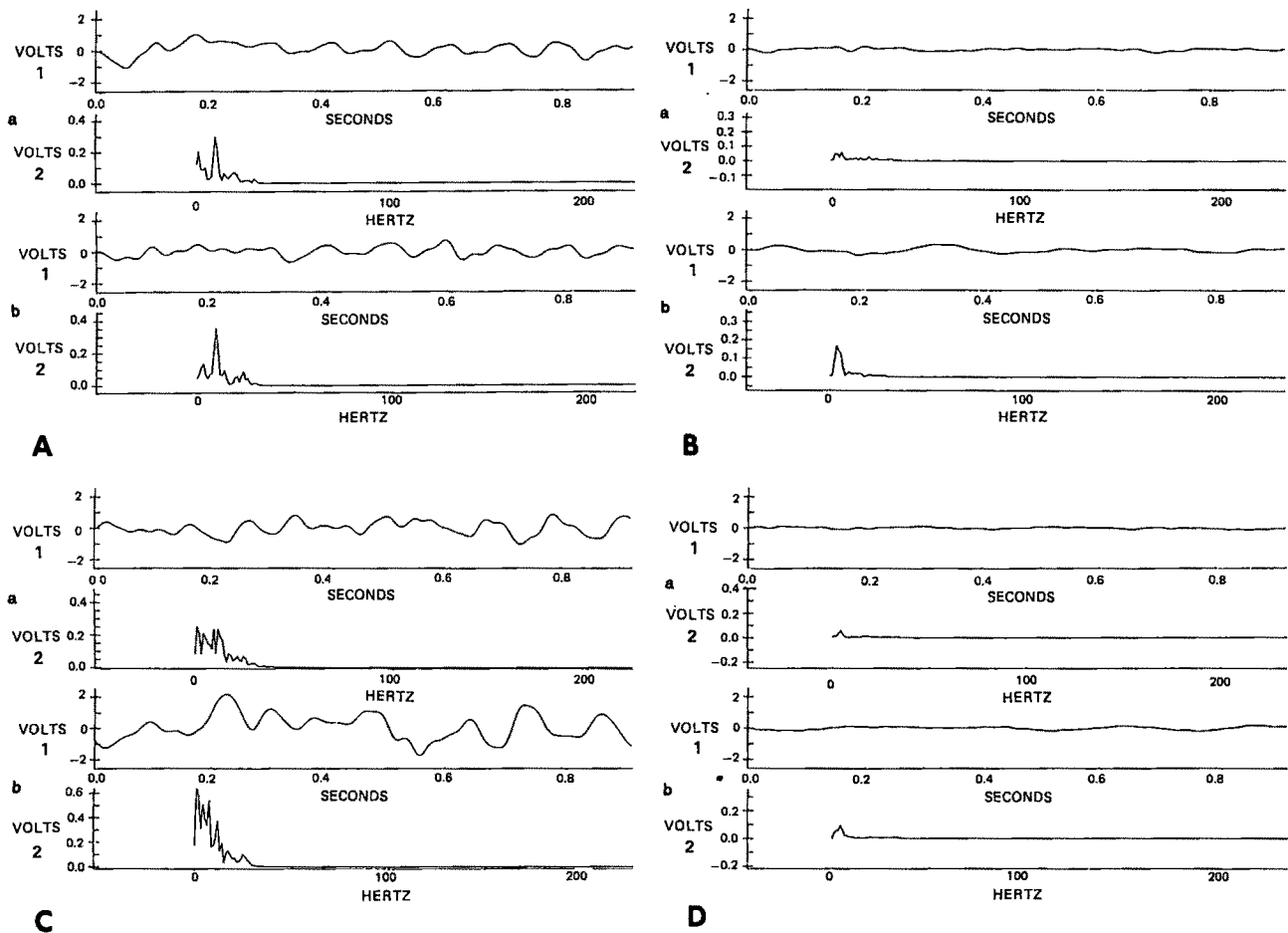


Fig 3. Demodulated amplitude (a: panel 1, contour; panel 2, spectra) and frequency (b: panel 1, contour; panel 2, spectra). A) (Subject 1) Patient with amyotrophic lateral sclerosis. B) (Subject 2) Control. C) (Subject 3) Patient. D) (Subject 4) Control.

the frequency band of flutter might provide further understanding of the site or physiology of the dysfunction producing it.

METHOD

From 32 patients with ALS identified as having rapid voice tremor or flutter on vowel prolongation, 8 (4 men and 4 women; ages 42 to 70 years) were chosen for analysis (Table 1). They were selected from the larger group of patients with ALS because of the unusual prominence of their tremor and their ability to sustain vowel prolongations for at least 10 seconds. An age- and sex-matched control group of 8 subjects was also selected for this study. All control subjects were free of neurologic disease or speech disorders of any kind.

From each subject's prolongation of the vowel /a/, an 8-second segment was chosen from reel-to-reel recordings and digitized at 20,000 samples per second into a 16-bit analog-to-digital converter to facilitate repeatability during analysis (Fig 2). These digitized segments were reconverted to analog at

20,000 samples per second through a 16-bit digital-to-analog converter and fed into the Vocal Demodulator, an instrument for analysis of low-frequency amplitude and frequency modulations.⁸ The amplitude and frequency demodulated signals were digitized into separate channels of a DATA 6000 Universal Waveform Analyzer. The 14-bit converter was set to 555 samples per second.

From each subject's 8-second amplitude and frequency signals, an FFT analysis was done on a 1-second segment identified perceptually as having apparent tremor or flutter. Because the amplitude and frequency of flutter varied within the 8-second sample, a 1-second analysis duration was selected to allow a precise sampling of the flutter and to avoid averaging the sample with tremor components. Spectral frequency resolution was 0.54 Hz. Dominant spectral peaks were identified in the range of 1 to 25 Hz by two experimenters. The frequency (Hertz) and amplitude (volts) for each peak were recorded and spectral data were plotted on an HP 7475A plotter. For the patients with ALS, peaks below 25% of the most prominent peak were excluded. All identifiable peaks were

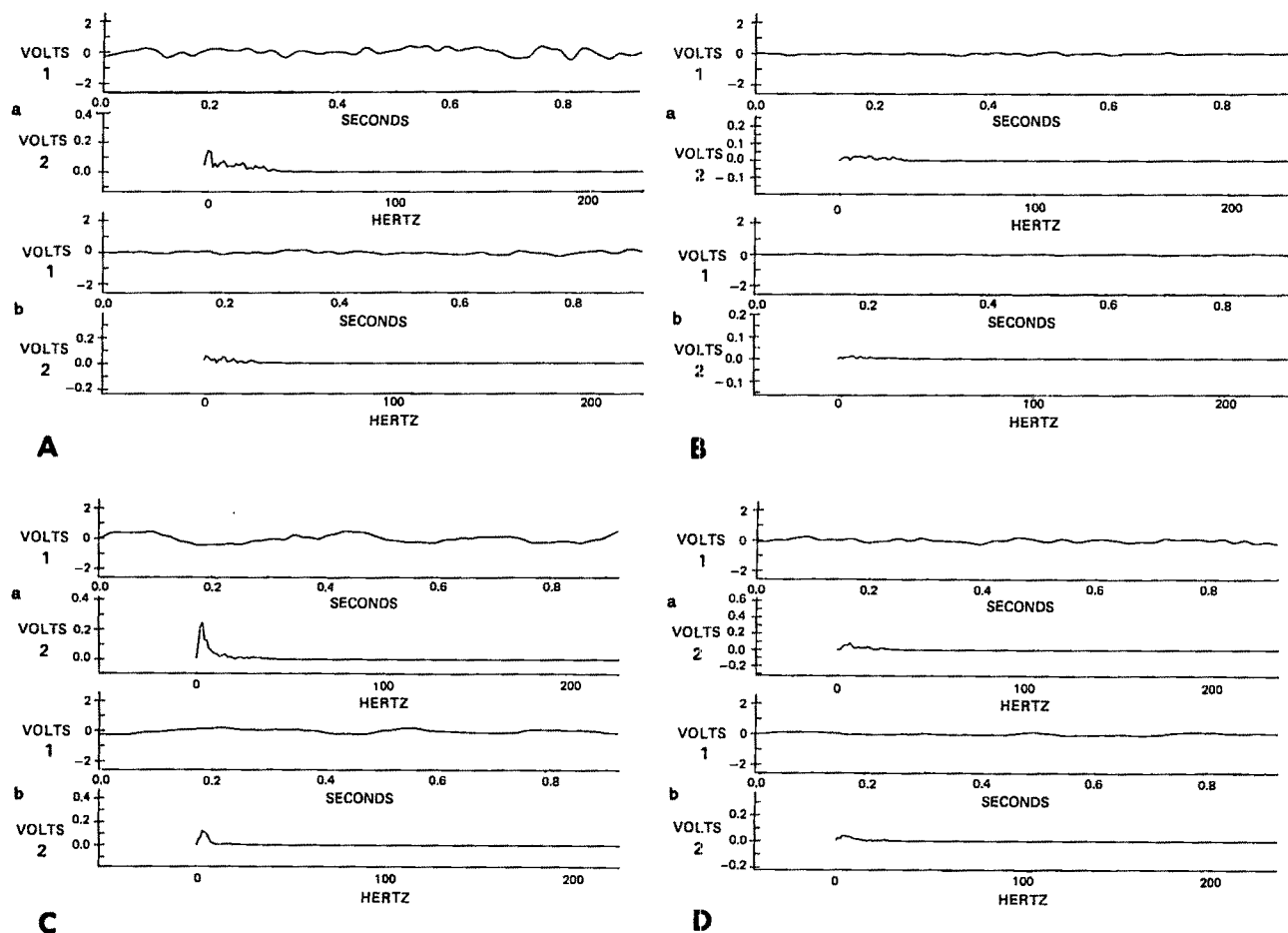


Fig 4. Demodulated amplitude (a: panel 1, contour; panel 2, spectra) and frequency (b: panel 1, contour; panel 2, spectra). A) (Subject 5) Patient. B) (Subject 6) Control. C) (Subject 7) Patient. D) (Subject 8) Control.

recorded for the control group. Seventy-five percent of the ALS and control data were reanalyzed for assessment of measurement reliability. Pearson product-moment correlation coefficients for repeated measures of these data are summarized in Table 2.

RESULTS

Waveform and spectral data for each patient with ALS and corresponding control subjects are given in Figs 3 through 6. Amplitude and frequency demodulation and corresponding spectra are represented in four traces. Panel a1 is the demodulated signal for amplitude, and panel a2 is the FFT of that signal. Panel b1 is the demodulated signal for frequency, and panel b2 is the FFT of that signal.

In patients with ALS, it is apparent that there were multiple combinations of levels and frequencies for amplitude and frequency modulations. For example, subject 1 (Fig 3A) had regular amplitude and frequency modulations at a single frequency. This finding was apparent in both the demodulated data according to waveform similarities (Fig 3A, panels a1 and b1) and the corresponding spectral data (Fig 3A,

panels a2 and b2). The prominent spectral peaks for both amplitude and frequency for this subject were 9.8 Hz. In contrast, subject 3 (Fig 3C) had prominent amplitude and frequency modulations, these occurring at various multiple frequencies. This observation was apparent both in the demodulated data, as demonstrated by the waveform dissimilarities (Fig 3C, panels a1 and b1), and in the corresponding spectral data (Fig 3C, panels a2 and b2). Multiple prominent spectral peaks for this subject's phonation ranged from 1.1 to 25 Hz for amplitude and from 1.1 to 17.4 Hz for frequency. Subject 3 (Fig 4A) had a higher level of modulation in amplitude than in frequency. This finding was apparent both in the magnitude dissimilarities of the demodulated waveforms (Fig 4A, panels a1 and b1) and in the corresponding spectral peaks (Fig 4A, panels a2 and b2).

In contrast to the patients with ALS, the control subjects had consistently low levels of modulations. Four of the eight control subjects (Figs 3B,D, 5D, and 6B) had a regular low-level frequency modulation, which is apparent in both the demodulated data and the spectral data. The prominent frequencies of these

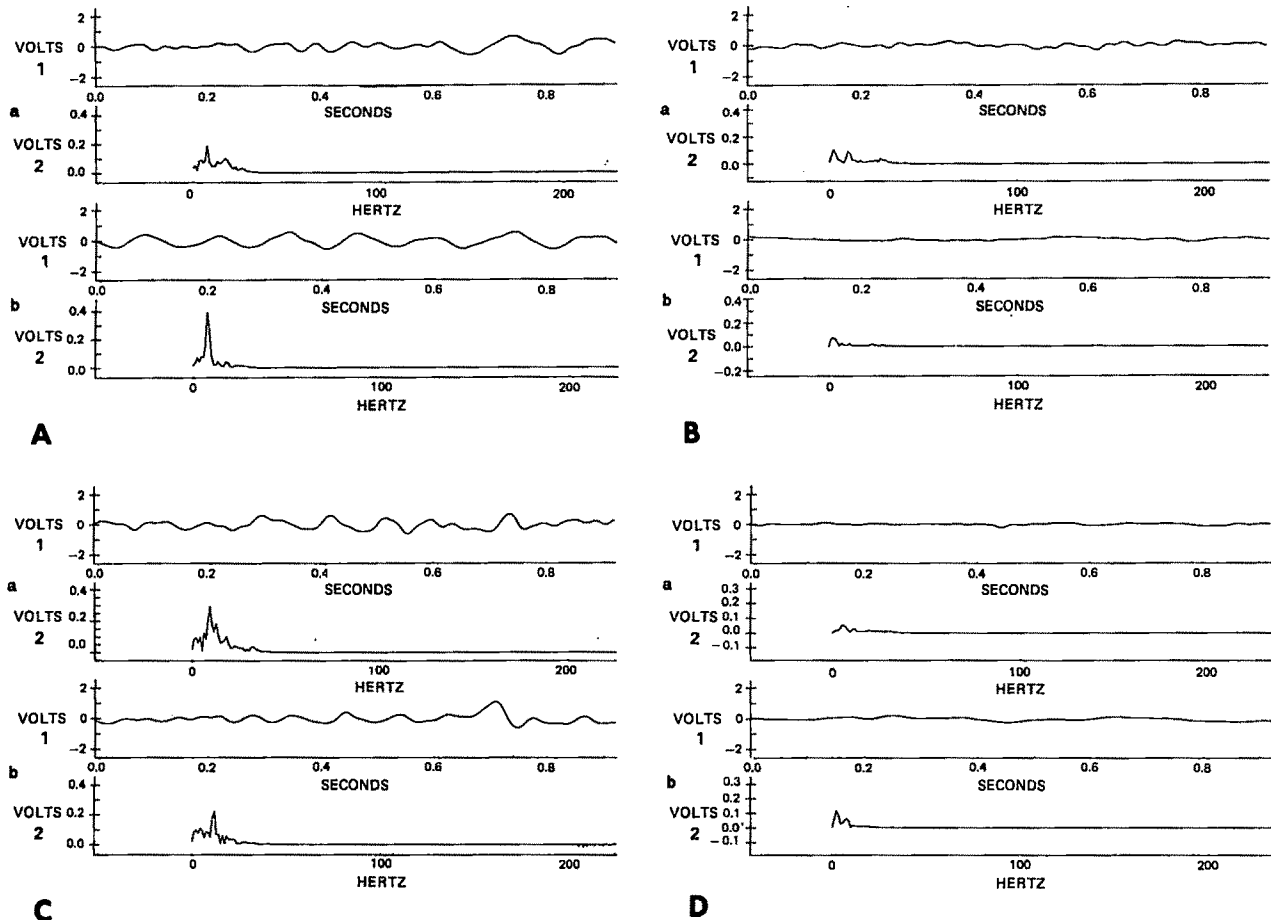


Fig 5. Demodulated amplitude (a: panel 1, contour; panel 2, spectra) and frequency (b: panel 1, contour; panel 2, spectra). A) (Subject 9) Patient. B) (Subject 10) Control. C) (Subject 11) Patient. D) (Subject 12) Control.

modulations ranged from 2.2 to 4.5 Hz.

Individual data for patients and controls are summarized in Table 3. These data include spectral peaks and levels measured for each subject. For patients with ALS, amplitude spectral peaks ranged from the cutoff frequency of 1.1 Hz to 25 Hz, and frequency peaks ranged from 1.1 to 23.9 Hz. For control subjects, amplitude spectral peaks ranged from 1.1 to 24.9 Hz, and frequency peaks ranged from 1.1 to 25 Hz. The amplitude of the spectral peaks for patients with ALS ranged from 32.5 to 400.0 mV for amplitude and from 17.7 to 637.0 mV for frequency. For controls, the amplitude of the spectral peaks ranged from 9.7 to 91.8 mV for amplitude and from 6.9 to 134.8 mV for frequency. Patients had an average of four to five peaks in amplitude and frequency per analysis, and controls had an average of three to four peaks.

DISCUSSION

To the experienced listener, the tremor or flutter during vowel prolongation in patients with ALS

sounds rapid, somewhere between 7 and 10 Hz. The intent of this study was to attempt to quantify these oscillations.

Results of demodulation and spectral analysis revealed that ALS patients with perceptible tremor or flutter produced both frequency and amplitude modulations of various frequencies and magnitudes. In certain patients, amplitude modulations were most apparent; in other patients frequency modulations were most apparent; and in still other patients frequency and amplitude modulations were equal and in phase. The prominent frequencies spanned the entire analysis range of 0 to 25 Hz; most patients had amplitude or frequency peaks within the range of 6 to 12 Hz. In contrast to the control subjects, the spectral peaks of the ALS patients were much more prominent.

The origins of these aberrant frequency and amplitude changes in the patients with ALS remain obscure. Although the ear hears these changes as some kind of tremor or flutter, quantification does not clearly establish that these fluctuations belong within

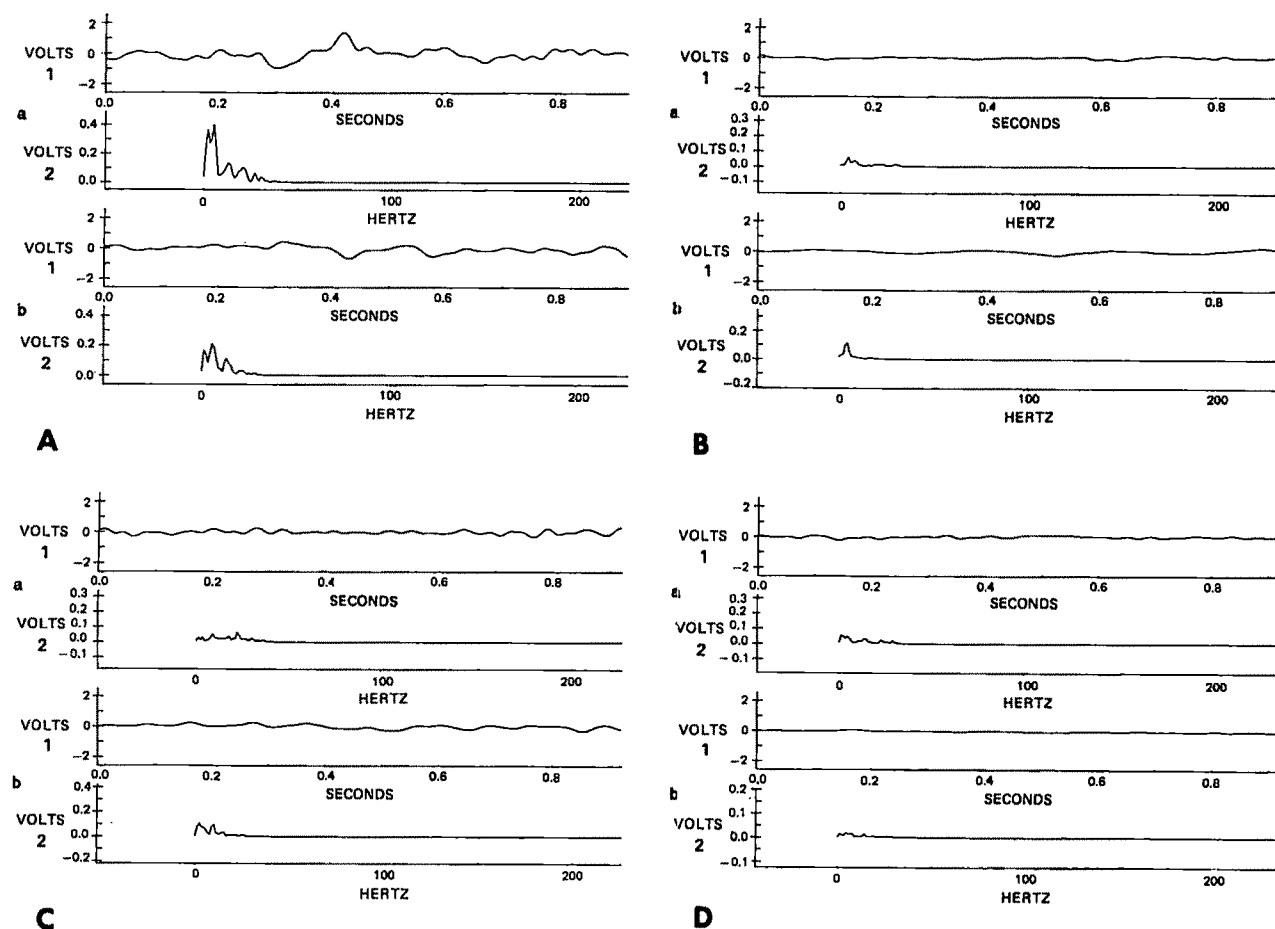


Fig 6. Demodulated amplitude (a: panel 1, contour; panel 2, spectra) and frequency (b: panel 1, contour; panel 2, spectra). A) (Subject 13) Patient. B) (Subject 14) Control. C) (Subject 15) Patient. D) (Subject 16) Control.

the classification of tremor, although whether they are may be a matter of semantics. Of interest, regardless of what these perturbations are called, is their origin. We are fairly certain that in patients with purely spastic (that is, pseudobulbar) bilateral upper motor neuron dysarthria, the dysphonia does not contain audible tremor, and in light of the fact that spasticity is the only other known supranuclear motor impairment in ALS, it seems unlikely that this flutter is of central origin. Alternatively, at the lower-motor neuron level there is evidence that patients who have peripheral neuropathy can have tremor within the range of 8 to 12 Hz.⁹ One explanation for its presence is that in subclinical peripheral neuropathy in which the stretch reflex is preserved, physiologic tremor is enhanced. In a study by Said et al¹⁰ of 14 patients with tremor associated with acquired peripheral neuropathies of different origin, all patients showed electrophysiologic evidence of denervation, minimal weakness, and tremor frequency in different limbs ranging from 4 to 12 Hz. (In none of these studies was voice tremor described.) One of the 14 patients with tremor in the study by Said et al had motor neuron disease

(ALS) involving both the central and the peripheral nervous systems.

In patients with polyneuropathy, a type of action tremor has been described involving peripheral muscles in which accelerometric tracings are synchronous with electromyographic activity at a rate of 6 to 8 Hz; with an improvement in the neuropathy, there is a reduction in the amplitude of the tremor.¹

Hence, we have an alternative to the hypothesis that the laryngeal and extralaryngeal tremor in ALS and peripheral neuropathy is due to an enhancement of physiologic tremor. The alternative explanation is that the tremor is a sign of loss of motor units resulting in intermittent absence of motor unit firing; when the absence of firing affects the intrinsic laryngeal muscles, it is perceived as a tremor or flutter. In our fiberoptic observations of the pharynx and larynx during flutter in ALS patients prolonging the vowel /a/, a rapid tremorous movement of the entire vocal tract could be clearly seen. The true vocal folds oscillated rapidly, as did the supraglottic musculature. Whether these tremorous movements were syn-

TABLE 3. FREQUENCY AND AMPLITUDE FOR AMPLITUDE AND FREQUENCY SPECTRAL PEAKS AND MEAN FUNDAMENTAL FREQUENCY

Subject	Category	Amplitude Spectral Peaks		Frequency Spectral Peaks		Fundamental Frequency (Hz)	Subject	Category	Amplitude Spectral Peaks		Frequency Spectral Peaks		Fundamental Frequency (Hz)			
		Frequency (Hz)	Amplitude (mV)	Frequency (Hz)	Amplitude (mV)				Frequency (Hz)	Amplitude (mV)	Frequency (Hz)	Amplitude (mV)				
1	ALS	1.1	204.5	3.3	134.4	286	9	ALS	4.3	92.6	7.5	389.7	122			
		4.3	99.2	9.8	352.7				7.7	186.9						
		9.8	298.5	14.1	95.0				13.0	82.3						
		19.5	69.1	23.9	87.9				17.4	101.8						
2	Control	2.2	91.8	1.1	106.4	245	10	Control	2.2	76.7	3.3	52.1	117			
		9.8	33.7	3.3	126.8				4.3	58.2	9.8	37.1				
				4.3	131.0				6.5	55.7						
				9.8	51.0				11.9	38.8						
3	ALS	1.1	249.8	1.1	637.0	326	11	ALS	2.2	94.3	2.2	97.7	175			
		4.3	209.2	4.3	507.0				4.3	96.9	4.3	109.4				
		9.8	231.7	7.6	540.0				6.5	124.7	7.6	86.6				
		11.9	234.3	11.9	370.7				9.8	293.0	11.9	222.2				
		17.4	85.7	14.1	190.3				13.0	181.7	16.3	56.6				
		21.7	68.0	17.4	126.4				18.4	100.3	18.4	57.3				
		25.0	69.5													
4	Control	4.3	42.7	3.3	134.8	268	12	Control	4.3	9.7	2.2	100.0	365			
		13.0	25.3	13.0	24.7				9.7	38.6	6.5	37.2				
		19.5	23.1						13	ALS	2.2	363.2		1.1	166.7	166
		24.9	24.3								5.4	400.0		5.4	209.2	
5	ALS	2.2	148.0	1.1	58.9	111	14	Control			1.1	35.3	3.3	112.4	198	
		5.4	60.6	2.2	51.4						5.4	48.6				
		9.7	76.1	5.4	34.4				10.9	24.4						
		16.3	55.5	7.6	30.2				16.3	22.4						
		19.5	62.4	9.7	52.5				23.8	17.8						
		23.9	32.5	10.9	43.5				15	ALS	1.1	30.3	2.2	106.0		166
				15.2	34.7						3.3	30.6	4.3	73.2		
6	Control	3.3	33.2	3.3	13.3	119	16	Control	7.6	27.5	7.6	28.1	105			
		8.7	29.7	7.6	15.8				10.9	22.0	10.9	18.6				
		14.1	18.3	18.5	7.3				14.1	35.4						
		17.4	20.3	25.0	6.9				20.6	15.9						
		22.7	11.0						23.8	18.3						
7	ALS	4.3	261.3	4.3	126.1	116										
8	Control	6.5	83.8	1.1	26.3	146										
		10.8	39.7	3.3	43.0											
		13.0	34.4	6.5	35.7											
		16.2	44.6	10.8	15.9											
		23.8	27.1	24.9	9.9											

Data were obtained from fast Fourier transform analysis of amplitude and frequency demodulated signals.

ALS — amyotrophic lateral sclerosis.

chronous with the voice tremor or flutter was not determined, and this issue needs to be explored,

electromyographically and acoustically, in future studies of this unusual phenomenon.

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HETEROGENEITY IN EPIDERMAL GROWTH FACTOR RESPONSIVENESS AND TUMOR GROWTH OF HUMAN MAXILLARY CANCER CELL LINES

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We have established three cell lines (IMC-2, IMC-3, and IMC-4) from a human maxillary tumor, which exhibited different sensitivities to epidermal growth factor (EGF). It was inhibitory to colony-forming abilities of IMC-3 and IMC-4 cells in culture, while it affected that of IMC-2 cells slightly if at all. The differential sensitivities to EGF among the three cell lines were reproducibly observed when several cell sublines were further established from tumors appearing in nude mice. Saturation-binding kinetics with ^{125}I -EGF showed similar levels of EGF-binding activities among the three cell lines. However, IMC-2, IMC-3, and IMC-4 showed almost similar sensitivities to cisplatin. Autophosphorylation of EGF receptor in the presence of EGF proceeded at similar levels among the three cell lines. Tumor growth was followed in nude mice when IMC-2, IMC-3, and IMC-4 at 1×10^7 cells were inoculated. The IMC-2 tumors enlarged at much faster rates than the other two cell lines. The IMC-4 tumors showed very slow growth rates, and IMC-3 tumors enlarged at an intermediate rate. These data suggest that the maxillary tumor used comprised cell populations that differed in their growth behaviors in response to EGF.

KEY WORDS — differential growth rates, epidermal growth factor responsiveness, human maxillary cancer.

INTRODUCTION

Epidermal growth factor (EGF) is important for many kinds of cells, including epidermal and epithelial cells.¹ It facilitates cell proliferation through interaction with the membrane-anchored glycoprotein receptor of molecular weight 170,000.² The EGF receptor gene is often amplified in human malignancies.³⁻⁶ An *src* family-related oncogene, *v-erb B*, is also known to encode a truncated form of EGF receptor.^{5,7,8} Overexpression of the EGF receptor gene or *erb B* gene causes transformation of mouse NIH3T3 cells.⁹⁻¹¹ Expression of functional EGF receptor is also required for malignant transformation by viral transforming genes: papilloma virus E5¹² and polyoma middle T antigen or *v-src*.¹³ Both EGF and EGF receptor are expected to be closely involved in malignant transformation as well as tumor growth.

We have previously established tumor cell lines from a patient with maxillary cancer, and these cell lines showed various levels of drug sensitivity to anticancer agents.^{14,15} In this study, we explore the possibility that a tumor comprises cell populations that differ in their growth rates. We established cell sublines from a tumor derived from a patient with maxillary cancer and examined the expression of EGF receptor in correlation with growth behaviors in vivo as well as in vitro in response to EGF.

MATERIALS AND METHODS

Materials. The EGF was obtained from Toyobo Corporation, Osaka, Japan. The ^{125}I -EGF was iodinated with Na ^{125}I by the chroline T method as described previously.¹⁶ An anticancer agent, cisplatin (*cis*-diamminedichloroplatinum), was obtained from Nihon Kayaku Company, Tokyo, Japan.

Cell Culture. Cells derived from a human solid tumor were grown in complete growth medium containing RPMI 1640 medium (Gibco Laboratory, Grand Island, New York), supplemented with 10% heat-inactivated fetal calf serum (Gibco), 100 U/mL of penicillin G, 100 $\mu\text{g}/\text{mL}$ of streptomycin, and 100 $\mu\text{g}/\text{mL}$ of kanamycin.¹⁵

Establishment of Cell Lines From Maxillary Cancer Patient. The patient was a 48-year-old man with a maxillary tumor (T3N0M0). The tumor was histologically well-differentiated squamous cell carcinoma. A tumor biopsy was performed before chemotherapy and irradiation and the specimen was cut into small pieces and subcutaneously transferred to nude mice. After 2 months, the tumor in the mice was extirpated and cultured in plastic flasks containing complete growth medium. To avoid contamination by mouse cells, the culture was performed in the presence of anti-nude mouse cell antiserum.^{14,15}

To establish several purified cell lines from the cultured tumor cells, 1×10^3 to 2×10^3 cells of the tumor were inoculated into 0.3% soft agar, and colonies appeared after incubation for 5 to 7 weeks at 37°C. About 10 colonies were independently isolated and each colony was grown in monolayer culture in a Petri dish. An independent colony being formed was purified from each Petri dish, and final-

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TABLE 1. MAXILLARY CANCER CELL LINES ESTABLISHED

Cell Lines	Original Cell Line	Derivations
IMC-2	—	Maxillary tumor
IMC-2-1	IMC-2	Tumor at inoculated site
IMC-2-3	IMC-2	Tumor in ascites
IMC-3	—	Maxillary tumor
IMC-3-5	IMC-3	Tumor at inoculated site
IMC-4	—	Maxillary tumor
IMC-4-5	IMC-4	Tumor at inoculated site
IMC-4-6	IMC-4	Tumor in bone marrow

ly we obtained three cell lines: IMC-2, IMC-3, and IMC-4.

The three cell lines were all found to show typical human karyotypes with hyperdiploid chromosomes. Cell lines IMC-2, IMC-3, and IMC-4 showed average chromosome numbers of 73 ± 11 , 57 ± 4 , and 56 ± 5 , respectively, when 29 to 40 metaphase chromosomes were analyzed. Determination of tumor growth in vivo in nude mice was carried out when all three cell lines were inoculated in nude mice according to a previous report.¹⁷ Each tumor cell line was inoculated at 1×10^7 .

Binding Assays. Human cell lines were seeded in 24-well plates and grown to a near-confluent state. For the ¹²⁵I-EGF binding assay, cells were washed twice with phosphate-buffered saline (PBS) and then incubated with 500 μ g of serum-free minimum essential medium (MEM) containing 20 mmol/L HEPES, 5 mg/mL bovine serum albumin, and ¹²⁵I-EGF in the presence or absence of a hundredfold excess of EGF for 2 hours at 4°C.^{16,18} Cells were then washed with PBS three times and lysed with 1% Triton X-100. The lysates were measured by a gamma counter. Specific ¹²⁵I-EGF binding was determined as the difference between the counts in the absence and presence of excess unlabeled EGF. For down-regulation assays for EGF binding, cells grown to near confluency in 24-well plates were pretreated with 10 ng/mL of EGF for 0, 4, and 24 hours, respectively; the cells were washed with PBS twice and incubated at 37°C for 2 hours in the binding buffer. After washing with binding buffer twice, 50 nmol/L of ¹²⁵I-EGF in the binding buffer was added in the presence or absence of excess competitor to assess nonspecific binding.

Receptor Phosphorylation. Confluent cells in 35-mm dishes were washed twice with phosphate-free MEM, then labeled with ³²P-orthophosphate (2.5 mCi/mL, Amersham Corp, Arlington Heights, Ill) in phosphate-free MEM for 1 hour. Then EGF (10 ng/mL) was directly added to the medium at 0, 15, 30, and 60 minutes before lysis. After labeling, the EGF receptors were immunoprecipitated with EGF receptor monoclonal antibody (B4G7) and purified by sodium dodecyl sulfate-polyacrylamide gel electrophoresis as described before.¹⁹

Colony Formation Assay. To assay colony forma-

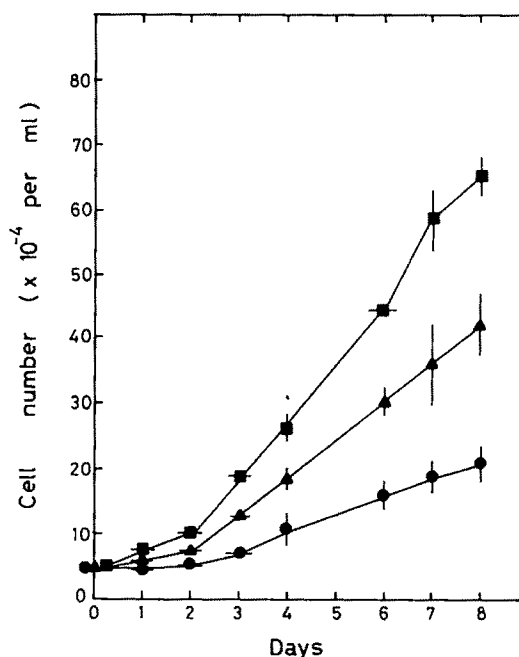


Fig 1. Comparison of growth curves of IMC-2 (circles), IMC-3 (triangles), and IMC-4 (squares), seeded at 5×10^4 cells per 60-mm dish and incubated at 37°C. Surviving cells were determined every day after trypan blue dye exclusion method. Bars indicate $\pm$ SD of triplicate dish.

tion, we first seeded 1,000 cells of all the cell lines in a 60-mm dish in the absence of any agents at 37°C for 18 hours, and then various doses of EGF and cisplatin were added and incubation continued for an additional 2 weeks. During incubation, every 4 days freshly prepared EGF or cisplatin was added. The colony number was counted after Giemsa staining.¹⁵

RESULTS

Establishment of Three Cell Lines From Single Tumor. Three serial cell lines (IMC-2, IMC-3, and IMC-4) were successfully cultured from a single case of maxillary cancer before cancer chemotherapy (Table 1). We have also established sublines from tumors in nude mice that were developed after inoculation of IMC-2, IMC-3, and IMC-4 cells, respectively (Table 1). The three cell lines showed different growth rates in culture (Fig 1). Cell lines IMC-2, IMC-3, and IMC-4 showed doubling times of about 70, 40, and 30 hours, respectively. Tumor growth in vivo was assayed in nude mice. As seen in Fig 2, IMC-2 showed much faster tumor growth than IMC-3 or IMC-4. Tumor sizes of IMC-2, IMC-3, and IMC-4 doubled every 17, 30, and 65 days. Tumor sizes (mm³) of IMC-2, IMC-3, and IMC-4 were estimated to be $2,300 \pm 760$, 560 ± 157 , and 45 ± 10 , respectively, at 50 days after inoculation. Cell line IMC-2 showed the slowest growth rate of the three cell lines in culture, whereas tumors of IMC-2 developed most rapidly in vivo.

Effect of Epidermal Growth Factor. The proliferation of tumor cells is stimulated or inhibited by

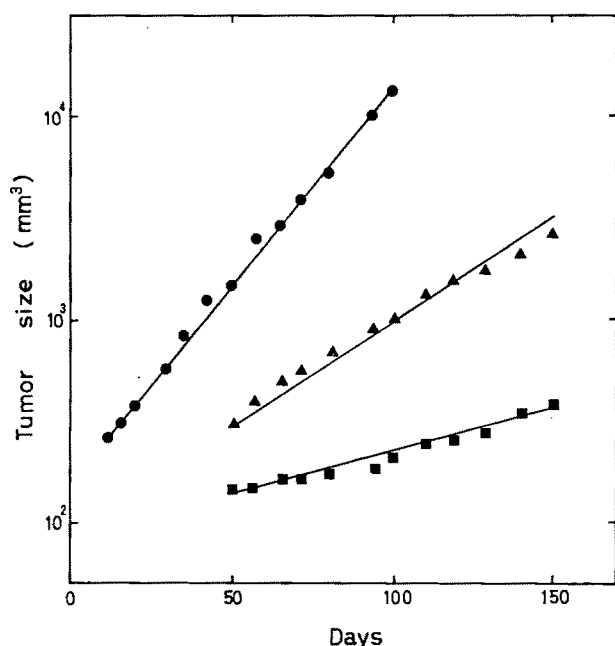


Fig 2. Time courses of tumor growth in vivo of IMC-2 (circles), IMC-3 (triangles), and IMC-4 (squares), subcutaneously inoculated at 1×10^7 cells into nude mice. At indicated periods, tumor sizes were determined. Each curve was deduced from mouse experiment with four to eight mice, and variations of tumor sizes were less than 30%. Tumor growth curves among IMC-2, IMC-3, and IMC-4 are significantly ($p < .01$) different.

various growth factors.²⁰ Cell growth of the three cell lines derived from a single tumor of a patient appeared to be different under different culture conditions. We thus examined whether EGF, transforming growth factor beta (TGF- β), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF) A, and PDGF B would affect growth of the three cell lines, and only EGF was found to affect cell growth (data not shown). We compared the effect of EGF on the cell growth of these three cell lines and their sublines derived from IMC-2, IMC-3, and IMC-4 tumors by colony formation assays. As seen in Table 2, addition of 0.1 ng/mL EGF reduced the surviving fraction by more than 50% of the initial fraction of IMC-3 and IMC-4, but only slightly reduced that of IMC-2. Colony formation of IMC-2 was blocked by only 30% by higher doses (0.5 to 1.0 ng/mL) of EGF. Sublines that were established from tumors developed in nude mice (Table 1) were also examined for their sensitivity to EGF. The EGF reduced the surviving fraction of one subline (IMC-3-5) derived from IMC-3 tumor and two sublines (IMC-4-5 and IMC-4-6) derived from IMC-4 tumor (Table 2). However, EGF did not reduce the surviving fraction of IMC-2-1 and IMC-2-3, derived from IMC-2 tumor. Enhanced sensitivities to the growth-inhibitory effects of EGF in IMC-3 and IMC-4 appeared to be maintained after passages of three cell lines in nude mice.

We also compared the effect of an anticancer

TABLE 2. DOSE RESPONSES OF COLONY FORMATION OF IMC CANCER CELL LINES TO EPIDERMAL GROWTH FACTOR

Cell Lines	Epidermal Growth Factor (ng/mL)			
	0	0.1	0.5	1.0
IMC-2	290.0 $\pm$ 3.6 (100)	269.3 $\pm$ 26.6 (93)	219.0 $\pm$ 28.5 (76)	227.0 $\pm$ 18.4 (77)
IMC-3	445.3 $\pm$ 20.5 (100)	145.0 $\pm$ 12.3 (33)	4.0 $\pm$ 0.0 (1)	6.3 $\pm$ 5.9 (1)
IMC-4	548.0 $\pm$ 27.7 (100)	230.0 $\pm$ 21.3 (42)	58.5 $\pm$ 11.0 (11)	39.3 $\pm$ 18.0 (7)
IMC-2-1	510.0 $\pm$ 1.0 (100)	453.7 $\pm$ 21.3 (89)	408.0 $\pm$ 49.0 (80)	366.3 $\pm$ 11.8 (72)
IMC-2-3	504.7 $\pm$ 26.3 (100)	481.7 $\pm$ 19.7 (95)	352.0 $\pm$ 6.2 (70)	309.7 $\pm$ 31.8 (61)
IMC-3-5	571.0 $\pm$ 45.4 (100)	256.3 $\pm$ 29.9 (45)	26.7 $\pm$ 0.6 (5)	16.7 $\pm$ 10.7 (3)
IMC-4-5	596.3 $\pm$ 16.2 (100)	396.0 $\pm$ 11.5 (72)	154.7 $\pm$ 19.0 (26)	124.7 $\pm$ 15.9 (21)
IMC-4-6	243.0 $\pm$ 3.8 (100)	69.3 $\pm$ 21.7 (29)	9.7 $\pm$ 6.4 (4)	3.0 $\pm$ 1.0 (1)

Number of colonies appearing after 2 weeks was calculated when 1,000 cells of each cell line were seeded. Each value is average of three dishes $\pm$ SD. In parentheses, surviving fraction for each cell line is presented as percentage; colony number of each cell line without epidermal growth factor was normalized as 100%.

agent, cisplatin, on formation of IMC-2, IMC-3, and IMC-4. As seen in Table 3, there appeared to be similar sensitivities to the cytotoxic effects of cisplatin among the three cell lines. We also observed similar sensitivities of these three cell lines to other anticancer agents, daunomycin and bleomycin (K. Matsui, unpublished data, 1989). The cellular sensitivities of IMC-2, IMC-3, and IMC-4 appeared to be rather specific against EGF.

Receptor Activities. We examined whether IMC-2, IMC-3, and IMC-4 were altered in their EGF receptor binding properties. As seen in Fig 3, IMC-2, IMC-3, and IMC-4 demonstrated both high- and low-affinity receptors for EGF. The number of EGF receptors in IMC-2, IMC-3, and IMC-4 was estimated to be 4.2×10^4 , 3.6×10^4 , and 1.3×10^4 per cell for high-affinity receptors and 2.6×10^5 , 2.3×10^5 , and 1.7×10^5 per cell for low-affinity receptors. Scatchard analysis also showed that the kilodalton values for the high-affinity binding were 7.4×10^{-10} mol/L (IMC-2), 7.5×10^{-10} mol/L (IMC-3), and 5.2×10^{-10} mol/L (IMC-4), and the low-affinity kilodalton values were 1.5×10^{-8} mol/L

TABLE 3. EFFECT OF CISPLATIN ON COLONY FORMATION OF THREE IMC CANCER CELL LINES

Cisplatin (ng/mL)	Cell Lines		
	IMC-2	IMC-3	IMC-4
0	387.0 $\pm$ 18.5 (100)	589.0 $\pm$ 1.0 (100)	456.0 $\pm$ 26.6 (100)
400	255.7 $\pm$ 19.6 (66)	488.7 $\pm$ 31.8 (83)	330.1 $\pm$ 21.5 (73)
800	115.3 $\pm$ 10.1 (30)	314.3 $\pm$ 13.6 (53)	198.3 $\pm$ 21.1 (44)
1,200	10.1 $\pm$ 5.1 (3)	26.2 $\pm$ 4.5 (4)	20.2 $\pm$ 8.1 (4)

Number of colonies appearing after 2 weeks was calculated when 1,000 cells of each cell line were seeded. Each value is average of three dishes $\pm$ SD. In parentheses, surviving fraction for each cell line is presented as percentage; colony number of each cell line without cisplatin was normalized as 100%.

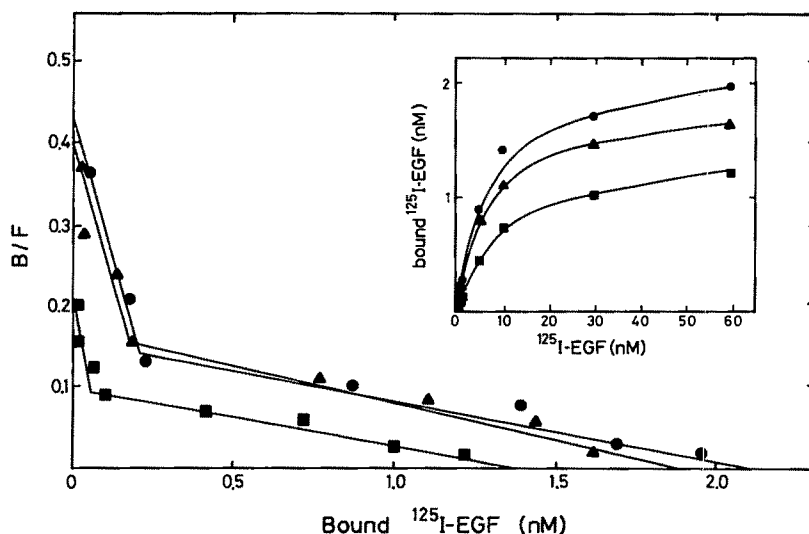


Fig 3. Scatchard analysis of ^{125}I -EGF binding to IMC-2 (circles), IMC-3 (triangles), and IMC-4 (squares) cells. Saturation binding kinetics for ^{125}I -EGF binding was determined for three cell lines at 4°C (see inset). EGF — epidermal growth factor, B/F — bound-to-free ratio.

(IMC-2), 1.2×10^{-8} mol/L (IMC-3), and 1.5×10^{-8} mol/L (IMC-4). Affinity values of EGF receptor binding were not significantly different among IMC-2, IMC-3, and IMC-4, but the number of EGF receptors appearing on the cell surface of IMC-4 was significantly different ($p < .01$) from that of the other two cell lines, ie, one third that of IMC-2 or IMC-3. Table 4 shows down-regulation of EGF receptor binding after exposure to EGF. There appeared similar levels of reduction of more than 70% in the EGF binding to the cell surfaces of IMC-2, IMC-3, and IMC-4 cells when they were exposed to EGF for 4 hours. There still was an inhibition of EGF binding after 24 hours of exposure to EGF (Table 4). Our recent metabolic labeling experiment with ^{35}S -methionine demonstrated that the precursor form of EGF receptor with 160 kd was almost completely converted into a mature form with 170 kd in IMC-2 cells.²¹ The metabolic labeling experiments showed similar rates of synthesis and maturation of EGF receptor in IMC-2, IMC-3, and IMC-4 cells, and the synthesis was almost completely down-regulated after exposure to 10 ng/mL EGF for 24 hours in the three cell lines (H. Mizoguchi and S. Shite, unpublished data, 1989).

We then examined whether the relatively increased resistance to EGF in IMC-2 cells was correlated with EGF receptor autophosphorylation. As seen in Fig 4, EGF receptors in the three cell lines were phosphorylated and their phosphorylation was enhanced by EGF. The phosphorylation activity was observed at similar levels in all three cell lines, and maximal activity was observed 30 minutes after exposure to EGF. The EGF receptor kinase activity of the three cell lines appeared not to differ.

DISCUSSION

Transforming growth factors such as TGF- α (or EGF) and TGF- β are secreted from malignantly transformed cells, and they are supposed to support

tumor growth.^{22,23} Transforming growth factor alpha is homologous to EGF, and binds to the same EGF receptor.^{22,24} The three cell lines derived from a tumor of a patient with maxillary cancer showed different sensitivities to EGF in culture. Epidermal growth factor inhibited the growth of IMC-3 and IMC-4 cells, but not that of IMC-2 cells. By contrast, these three cell lines showed similar sensitivities to the cytotoxic effects of an anticancer agent, cisplatin. Our previous studies have demonstrated that several cell lines established from a tumor of a patient with maxillary cancer showed different sensitivities to the cytotoxic effects of anticancer agents, suggesting cell populations that are heterogeneous with respect to drug sensitivities.^{14,15} Our present study apparently demonstrates that a tumor comprised cell populations that differed in their growth responses to EGF.

The growth curves of IMC-2, IMC-3, and IMC-4 show doubling times of 70 hours, 40 hours, and 30 hours, respectively, in culture. By contrast, tumors of the three cell lines double in size in 17 days for IMC-2, 30 days for IMC-3, and more than 65 days for IMC-4. The growth rates of IMC-2 and IMC-4 cells in vitro have an inverse relationship to the tumor growth rates in vivo. The cell growth of IMC-4 is highly susceptible to the growth inhibition

TABLE 4. EFFECT OF EGF ON EGF RECEPTOR BINDING ACTIVITIES

Exposure to EGF (h)	EGF Binding (cpm/ 10^6 cells)		
	IMC-2	IMC-3	IMC-4
0	76,880 (100)	68,136 (100)	40,850 (100)
4	21,852 (28)	19,142 (28)	10,623 (26)
24	30,809 (40)	27,088 (40)	20,422 (50)

Three cell lines were exposed to 10 ng/mL EGF for indicated time, and then EGF binding assays were performed. Each value is average of duplicate dishes, and values varied less than 5%. In parentheses, relative binding activities are presented as percentage; 100% corresponds to binding activity in absence of preexposure to EGF.

EGF — epidermal growth factor.

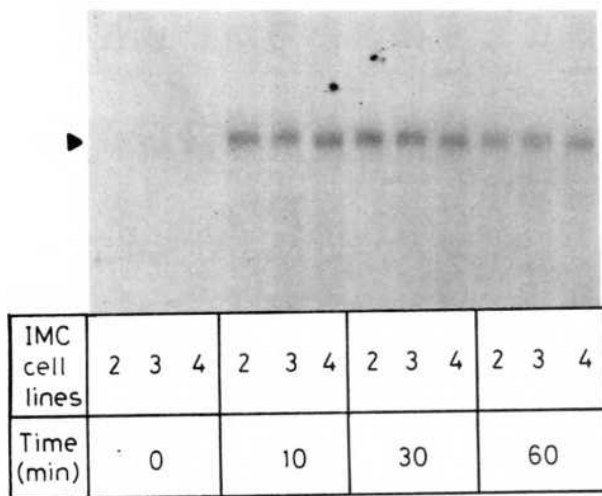


Fig 4. Effect of epidermal growth factor (EGF) on phosphorylation of EGF receptor. IMC-2, IMC-3, and IMC-4 cells were labeled *in vivo* with ^{32}P -orthophosphate in presence of 10 ng/mL EGF for indicated periods. Cells were then lysed and immunoprecipitation of EGF receptor was performed with anti-EGF receptor antibody. Electrophoresis was carried out by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (7%). Arrowhead — position of EGF receptor.

of EGF, but that of IMC-2 is not. The slow growth rates of IMC-4 tumor might be due to the high susceptibility to growth inhibition of EGF in mice *in vivo*. The blood concentration of EGF is estimated to be 1 to 3 ng/mL in mice,²⁵ which is sufficient to affect proliferation of IMC-3 or IMC-4 cells.

Epidermal growth factor shows growth inhibition of some cell lines and growth stimulation of other cell lines with an ordinary number of EGF receptors. At concentrations mitogenic for other cells, EGF is found to be markedly inhibitory for

the growth of the epidermoid carcinoma cell line A431,^{26,27} which possesses an extremely high number of EGF receptors²⁸; A431 cells have approximately 10 times the number of EGF receptors that IMC-2, IMC-3, and IMC-4 cells do. In most cell lines with EGF-resistant variants from the EGF-sensitive cells, reduced levels of EGF receptor expression are found in comparison with their parental counterpart cells.²⁹⁻³¹ Hirai et al³² have reported that EGF receptor hyperproducing cells escape the EGF-mediated growth inhibition because of dual pathways: the loss of EGF receptor expression and the efficient down-regulation of the cell surface EGF receptors. Concerning the possibility of the down-regulation of EGF receptor activity, EGF receptor activity of EGF-resistant IMC-2 cells is reduced to similar levels as in EGF-sensitive IMC-3 and IMC-4 cells (Table 4). The number of EGF receptors in IMC-4 cells was one third that in IMC-2 or IMC-3 cells. These results demonstrate that there appear to be no significant changes in EGF receptor expression among the three cell lines. The binding of EGF to the receptor induces autophosphorylation of the EGF receptor.³³ The EGF receptors of IMC-2, IMC-3, and IMC-4 cells are phosphorylated at similar levels in the presence of EGF (Fig 4). The differential responses to EGF among the three cell lines might be mediated through a postreceptor process. In fact, EGF-induced signaling appears to differ between IMC-2 and IMC-3 or IMC-4, because expression of plasminogen activator inhibitor 1 in response to EGF was specifically altered in IMC-2 cells (H. Mizoguchi et al, manuscript in preparation). Further study is in progress on how the growth of these IMC-2, IMC-3, and IMC-4 cell lines is modulated by EGF.

ACKNOWLEDGMENT — The authors thank Michihiko Kuwano, MD, of Oita Medical School for fruitful discussion.

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VESTIBULO-OCULAR COMPENSATION FOLLOWING UNILATERAL VESTIBULAR DEAFFERENTATION

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Vestibulo-ocular compensation following vestibular deafferentation was investigated in 26 acoustic neuroma patients following tumor removal and in 5 Meniere's disease patients following vestibular nerve section by using sinusoidal harmonic acceleration testing. All three test parameters (phase lead, gain, and asymmetry), when averaged, shifted significantly on the first postoperative test (average 0.4 months after operation). A marked progression in central compensation with gain returning to the range of normal control values was seen in the tests performed 1 to 6 months (average 2.6 months) postoperatively. However, phase lead and asymmetry (especially at 0.01, 0.02, 0.04, and 0.08 Hz) remained outside the range of normal control values, and all three parameters failed to return to their preoperative level even when tested at more than 12 months (average 20.2 months) after operation. This finding indicates that the deficits of the vestibulo-ocular reflex to head acceleration are of long duration if not permanent.

KEY WORDS — sinusoidal harmonic acceleration, vestibular neurectomy, vestibulo-ocular compensation, vestibulo-ocular reflex.

Vestibular deafferentation creates a syndrome of ocular motor and postural deficits. The postoperative symptoms usually subside over time because of central compensation. Vestibular compensation following labyrinthectomy has been widely studied in animals^{1,2} and humans.^{3,4} The sinusoidal harmonic acceleration (SHA) test provides an objective and accurate monitor for vestibular abnormalities^{5,6} and is more sensitive than conventional electronystagmography testing.⁷ The purpose of this study was to investigate vestibulo-ocular reflex (VOR) compensation of the central nervous system following unilateral vestibular deafferentation and to monitor this process by using low-frequency SHA testing in the early and intermediate postoperative stage. We were especially interested to see if there is a recognizable pattern of compensation seen with SHA testing after vestibular injury that may be also useful as a less subjective way of monitoring other forms of vestibular insult, particularly when worker's compensation claims are being assessed.

SUBJECTS AND METHODS

Ninety-three SHA tests were performed on 31 patients, 26 of whom had acoustic neuromas surgically removed and 5 of whom had Meniere's disease

and vestibular nerve sections (Table 1). The patients' ages ranged from 24 to 76 years (average 52) with 14 women and 17 men and 14 left ears and 17 right ears. The tumor size varied from 0.7 cm to 4 cm (average 2.2 cm). There were no symptoms or signs of brain stem damage after operation, except in one patient, who had some pontine trauma due to removal of a particularly adherent tumor. Twenty-nine patients were tested preoperatively. Sixty-four tests were performed postoperatively. The postoperative test time varied from 1 week to 3.6 years. The tests were grouped as follows: first postoperative test, which was within 1 month of operation; 1 to 6 months; 6 to 12 months; and greater than 12 months. The distribution of the average postoperative test times is shown in Table 2.

The SHA test was performed with a computerized rotatory chair system (Contraves-Goerz model 403 D) using low-frequency oscillation stimuli of 0.01, 0.02, 0.04, 0.08, and 0.16 Hz at a constant peak velocity of 50°/s. The acceleration varied from 3°/s² to 50°/s² at 0.16 Hz. The patient was seated in a light-attenuated booth with the head supported and tilted forward 30° to bring the lateral semicircular canals into the plane of rotation. The tester monitored the patient and eye movements using an infrared camera with a television monitor. Constant voice contact was made with the patients to maintain their alertness. The eye movements were recorded by standard electro-oculographic techniques

TABLE 1. PREOPERATIVE AND POSTOPERATIVE SINUSOIDAL HARMONIC ACCELERATION TESTS

Group	N	Pre	Postoperative Test				Total Tests
			<1 mo*	1-6 mo	6-12 mo	>12 mo	
A	26	25	13	18	10	12	78
B	5	4	4	3	0	4	15
Total	31	29	17	21	10	16	93

Pre — preoperative test, A — acoustic neuroma resection, B — Meniere's disease with vestibular nerve section.

*First postoperative test.

TABLE 2. DISTRIBUTION OF POSTOPERATIVE TEST TIMES (n = 93)

	<1 mo*	1-6 mo	6-12 mo	>12 mo
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Average postoperative time (mo) 0.4 2.6 7.8 20.2

*First postoperative test.

From the Department of Otolaryngology, Alfred Hospital, Melbourne, Australia.

REPRINTS — Robin Hooper, FRACS, Dept of Otolaryngology, Alfred Hospital, Commercial Rd, Prahran, Victoria 3181, Australia.

TABLE 3. AVERAGED PHASE LEAD FINDINGS
IN DEGREES (n = 93)

	0.01 Hz	0.02 Hz	0.04 Hz	0.08 Hz	0.16 Hz
Pre Op	59.902	40.212	25.588	16.005	7.188
<1 mo*	76.749	56.870	37.160	27.564	14.140
1-6 mo	71.193	53.306	34.669	20.979	10.883
6-12 mo	74.078	54.559	35.631	21.305	6.994
>12 mo	68.868	48.879	32.387	17.981	8.197
Pre Op — preoperative test.					
*First postoperative test.					

with electrodes placed at both outer canthi. Calibrations were performed before each test frequency. The results were compared with our normal data.⁸ Phase lead values greater than the mean + 2 SD, gain values less than the mean - 2 SD, and asymmetry values outside of the mean $\pm$ 2 SD were identified as being abnormal.

The patient who had brain stem injury during acoustic neuroma removal underwent a formal physical therapy rehabilitation program. All other patients used a self-administered program of exercise and increasing mobility. Only three had not returned to their preoperative occupations by the seventh month after operation — in two cases for reasons other than vestibular disturbance.

RESULTS

The results of phase lead, gain, and asymmetry are summarized in Tables 3-5 and are graphed in the Figure. The results of the patient with pontine trauma were not significantly different from those of the others in the study and have been included.

The averaged phase lead was outside the range of normal control values at the three lower test frequencies in the preoperative tests. It was significantly increased at all of the five test frequencies in the first postoperative tests. The phase lead tended to decrease in the later postoperative retests, but never returned to the preoperative level and remained outside of the range of normal control values, especially at the lower test frequencies (0.01, 0.02, 0.04, and 0.08 Hz), even after 12 months (see Figure, A).

The averaged gain was within the range of normal control values (mean - 2 SD) in the preoperative tests at all test frequencies. It markedly decreased at the four lower test frequencies on the first postoperative tests. An apparent gain increase was seen on the 1- to 6-month postoperative tests. It failed to return to the preoperative level after an average time of 20.2 months postoperatively, although it remained within 2 SD of the mean of normal control values (see Figure, B).

Asymmetry was generally in the range of normal control values for the preoperative group (see Figure, C). It shifted markedly at all test frequencies in the first postoperative tests and then returned to-

TABLE 4. AVERAGED GAIN FINDINGS
AS RATIO (n = 93)

	0.01 Hz	0.02 Hz	0.04 Hz	0.08 Hz	0.16 Hz
Pre Op	0.312	0.521	0.636	0.685	0.651
<1 mo*	0.146	0.298	0.247	0.426	0.474
1-6 mo	0.211	0.387	0.513	0.632	0.627
6-12 mo	0.209	0.397	0.520	0.641	0.601
>12 mo	0.277	0.409	0.488	0.589	0.527
Pre Op — preoperative test.					
*First postoperative test.					

ward the preoperative level in all subsequent tests, particularly in the 1- to 6-month group. There was, however, no return to the range of normal control values (mean $\pm$ 2 SD), and the averaged response remained beyond the preoperative levels even in the last test.

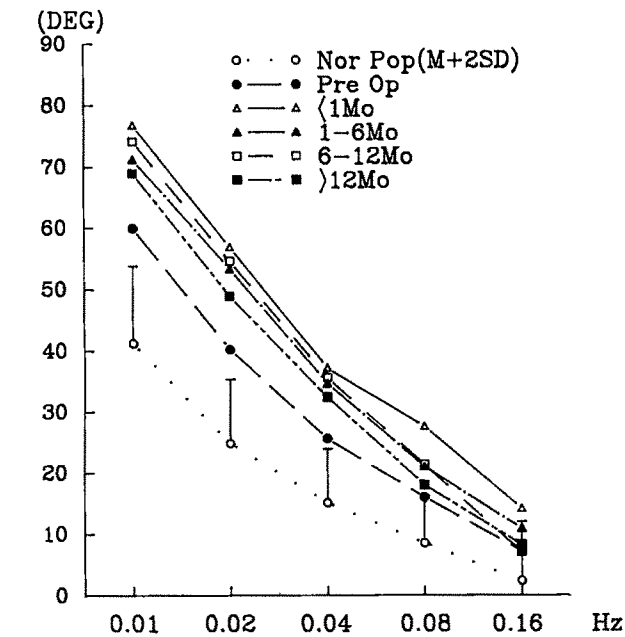
DISCUSSION

An acoustic neuroma removal and a vestibular nerve section, although different operative procedures, have the same effect on the VOR arc structure by detaching the peripheral vestibular receptor apparatus from its central connections. Vestibular compensation following vestibular deafferentation is due to the plasticity of the central nervous system; however, the exact mechanisms are not fully understood. Animal experiments have shown that labyrinthine destruction is followed by reactivation of activity in the ipsilateral vestibular nuclei.¹ This reaction is a major contributor to compensation for static signs like spontaneous nystagmus and head roll tilt. Cerebellar input inhibits vestibular activity on the normal side, producing a degree of symmetry in the vestibular information within the two halves of the system.² Smith and Curthoys⁹ have shown that a significant recovery in resting activity occurs in the ipsilateral vestibular nuclei by the time signs such as spontaneous nystagmus and head roll tilt have largely disappeared.

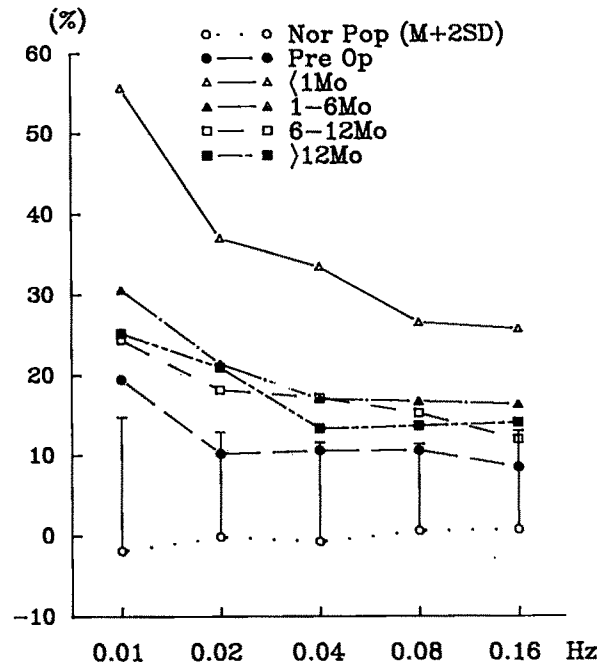
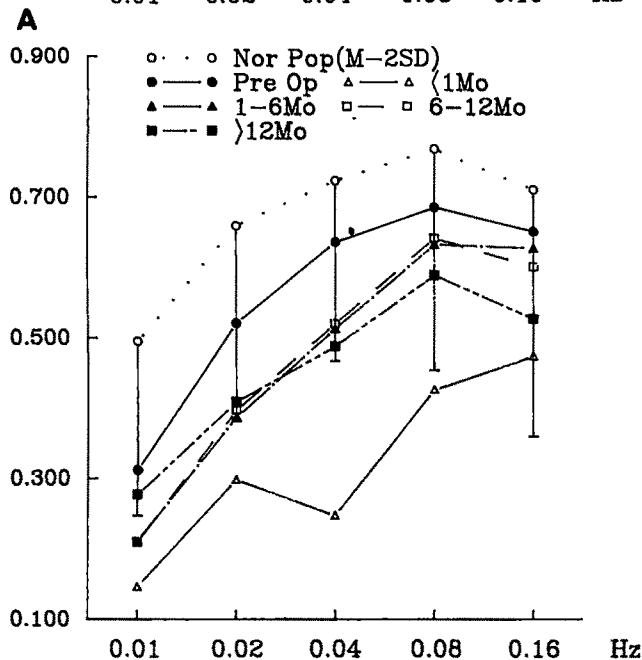
All three test parameters in this study changed significantly as shown by a comparison of the preoperative tests with the first postoperative tests and were outside the range of normal control values (mean + 2 SD) at all five test frequencies. These results correlate with the morphological findings in 8-week and 1-year postneurectomy cats that showed that few type I neurons remained, there is a more than 70% reduction in the number of synaptic profiles of the vestibulo-ocular cell soma,¹⁰ and there is low resting activity in the type II neuron of

TABLE 5. AVERAGED ASYMMETRY FINDINGS
IN PERCENT (n = 93)

	0.01 Hz	0.02 Hz	0.04 Hz	0.08 Hz	0.16 Hz
Pre Op	19.449	10.177	10.550	10.513	8.427
<1 mo*	55.631	36.941	33.360	26.412	25.602
1-6 mo	30.597	21.397	16.970	16.636	16.253
6-12 mo	24.331	18.098	17.128	15.133	11.859
>12 mo	25.174	20.916	13.283	13.580	14.000
Pre Op — preoperative test.					
*First postoperative test.					



Averaged results. Nor Pop — normal population. Pre Op — pre-operative test. A) Phase lead. B) Gain. C) Asymmetry.



the ipsilateral medial vestibular nuclei.¹¹ The gain loss reflects a loss of neuronal stimulus response on the side of the lesion, and the resulting asymmetry is caused by lack of background activity derived from the vestibular nerve.¹²

Fetter and Zee¹³ reported that in rhesus monkeys the VOR gain diminished from 1.0 to 0.5 on the first measurement after labyrinthectomy (18 to 20 hours postlesion), then increased rapidly within a few days postoperatively to reach values ranging from 0.61 to 0.98 by 3 months postoperatively. In this study, the most significant progression of central compensation occurred in the 1- to 6-month (average 2.6 months) postoperative tests, as evi-

denced by reduction in phase lead and asymmetry, with the gain returning to the range of normal control values.

Fetter and Zee¹³ also reported that labyrinthectomy chronically impairs the action of the vestibular velocity-storage mechanism. Maioli et al¹⁴ found that the VOR dynamics showed significant long-term deficits as measured in the dark in unilateral vestibular nerve lesions in the cat up to 22 months postoperatively. Smith and Curthoys¹⁵ stated that the normal average resting activity in the guinea pig is restored in type I neurons in the ipsilateral and contralateral medial vestibular nuclei. However, 52 to 60 hours after operation, the gain and the phase

of the response of these neurons to horizontal sinusoidal acceleration were abnormal and they remained so up to 8 to 12 months postoperatively. Long-term impairment following vestibular deafferentation has also been reported in humans. Shotton et al¹⁶ found a persistent spontaneous jerk nystagmus in all six Meniere's patients who had undergone vestibular nerve section 3.5 years (average) previously, even though they were free of marked vestibular symptoms. Katsarkas and Segal¹⁷ reported a group of well-compensated patients who had undergone unilateral surgical ablation of peripheral vestibular function; their initial postoperative symptoms and signs (namely, vestibular gaze stabilization deficits to rapid head movement) recurred under certain conditions. The long-term abnormalities of phase lead and asymmetry shown in this study support these previously reported results in animals¹³⁻¹⁵ and findings in humans.^{16,17} Furthermore, all three test parameters failed to return to the preoperative level after a prolonged period; this finding suggests that the VOR compensation following detachment of the peripheral vestibular receptor apparatus (vestibular neurectomy or labyrinthectomy) may be long-term and incomplete.

The results of this study are similar to those reported by Baloh et al.³ Black et al⁴ have presented similar results; however, their gain values showed only minimal reduction immediately following operation. A possible explanation could be the different test frequencies used in their study. Low-frequency sinusoidal rotational stimuli were used in testing the subjects of this paper and that of Baloh et al, whereas pseudorandom rotations consisting of frequencies from 0.0092 to 0.766 Hz were used in the study by Black et al. Baloh et al showed that the

gain was decreased and phase lead increased at the low-frequency stimuli, but both approached normal levels at the high-frequency stimuli (>0.4 Hz) in patients with chronic compensated (mean duration of 1.1 year) unilateral and bilateral peripheral vestibular lesions; this finding suggests that high-frequency rotational testing may not show the deficits that appear at lower frequencies. The average phase lead and asymmetry failed to reach the preoperative mean level in both the current study and that reported by Black et al, although they did tend to return toward the preoperative mean level.

CONCLUSIONS

Following vestibular deafferentation, there is an immediate significant increase in phase lead, a decrease in gain, and a marked shift in asymmetry at all five test frequencies. As central compensation progresses, there is a return of phase lead, gain, and asymmetry toward preoperative levels. This is most apparent in the 1- to 6-month (average 2.6) postoperative tests, with gain returning to the range of normal control values (mean - 2 SD). However, the averaged phase lead and asymmetry remained abnormal and none of the three test parameters returned to the preoperative level even 20.2 (average) months after operation. This finding indicates that the deficits to the head acceleration are of long duration if not permanent.

There is a predictable progression of findings on SHA testing when compensation for vestibular deafferentation is followed. This trend follows the patient's clinical recovery and may have use in monitoring and documenting the recovery of other patients with vestibular deficits, especially those in whom a more "objective" assessment is required.

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READING SKILLS AND AUDITORY PROCESSING ABILITY IN CHILDREN WITH CHRONIC OTITIS MEDIA IN EARLY CHILDHOOD

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The effect of recurrent middle ear disease during the first 2 years of life on auditory perceptual skills and reading ability was examined in two groups of 6- and 7-year-old children who were pair-matched by age, gender, socioeconomic status, and receptive vocabulary. Group 1 consisted of children with documented chronic otitis media at an early age, and group 2 had no history of middle ear problems. Tests of auditory perceptual skills and reading ability were administered. Significant differences in performance on all tests of auditory processing ability and reading ability were noted.

KEY WORDS — academic performance, auditory perceptual skills, auditory processing skills, ear infections, otitis media, reading ability.

INTRODUCTION

Recently, much interest has been expressed in the effects of chronic otitis media. The possibility of deleterious effects on speech and language development and auditory processing ability has been examined, but the results are inconclusive.¹⁻¹⁰ Brandes and Ehinger⁶ observed significantly poorer performance in auditory perceptual abilities of children with histories of early chronic otitis media than in their peers. Hoffman-Lawless et al⁵ reported no differences in auditory processing abilities of 7- and 9-year-old children with and without early recurrent ear infections. However, most of the children in the latter study classified as having chronic otitis media acquired their disease between their second and fourth years. As the authors note, central auditory deficits may be more inclined to occur in otitis-prone children who acquire middle ear effusion during the first few months of life, when the auditory nervous system is still developing. The question concerning the effects of early recurrent otitis media before the age of 2 years, therefore, has not been answered.

The question of whether early chronic otitis media may have adverse effects on academic achievement has been addressed.¹⁰⁻¹² The results, again, are debate-worthy. Zinkus and Gottlieb¹⁰ and Silva et al,¹¹ who found significantly poorer reading ability in children with histories of recurrent ear infections, did not control for the hearing sensation level of the test items, despite the fact that many of the children in their experimental group had ear infections at the time of the study. Brandes and Ehinger,⁶ who did compensate for the degree of hearing loss by presenting all test items at a standard 45 dB sensation level, found no significant difference in reading ability in

children with chronic otitis media. However, the authors did note that the school district from which their samples were drawn placed heavy emphasis on reading and that a great number of their group with chronic conductive hearing loss received the services of support personnel. Lous and Fiellau-Nikolajsen¹² also found no effect on reading related to the presence of recurrent middle ear disease. Their subjects, however, were studied beginning at the age of 3 years, and no consideration was given to the presence of ear disease during the first 3 years of life — a period critical for speech and language development. In addition, the testing for basic reading skills was done on an entirely visual test with no requirement to deal with auditory input.

The research on the possible effects of early chronic otitis media on reading and auditory perceptual skills is inconclusive because of numerous methodological problems. The present study attempted to assess the effects of early recurrent middle ear problems on auditory perceptual skills and reading ability.

SUBJECTS

Forty-eight children, 6 and 7 years of age and enrolled in regular first and second grades in the Muncie Community School System, participated in the study.

To ensure that differences in hearing status at the time of the study did not confound the results of the study, and also to determine that each subject performed at his or her optimal level, all children had to pass a hearing screening test at 10 dB hearing level at the octave frequencies 250 to 4,000 Hz. All subjects had middle ear pressure between 0 and -200 mm H₂O

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and static compliance between 0.3 and 1.5 cm³ of equivalent volume of air. In order to be included in this study, each child had to pass a visual screening test including fusion, far and near vision, muscle coordination, and color blindness on a Titmus Test. The use of this criterion allowed for an evaluation of the auditory perceptual skills and reading skills without a confounding variable of visual perceptual dysfunction. All of the children had passed a speech-language screening test performed by the school speech-language pathologist. None of the children exhibited any obvious mental retardation, congenital abnormality, or chronic illness at the time of the testing. By using only children with normal speech and language and no learning disabilities, any differences obtained between the experimental and control groups can be attributed to the presence or absence of early chronic otitis media and not to other causes for speech-language problems and learning disabilities. It is recognized that this group of chronic otitis media children represents a distinct subset of the chronic otitis media patient population.

The subjects were divided into two groups: a normal-hearing control group (NG; 12 boys and 12 girls) and a chronic conductive hearing loss experimental group (CG; 12 boys and 12 girls). The subjects in each group were pair-matched according to age, gender, grade level, receptive vocabulary level (as measured by scores on the Peabody Picture Vocabulary Test (PPVT; revised form M), so that any differences between the groups could not be attributed to these variables. The mean age for the NG was 6.93 years and the mean age for the CG was 6.77 years. The analysis of variance indicated no statistically significant difference between the ages of the two groups. The mean PPVT percentile rank for the NG was 61.71, and for the CG it was 56.71. The analysis of variance indicated no statistically significant difference between the two groups on the PPVT.

The CG consisted of children who had a positive history of middle ear problems with the initial episode before 2 years of age as verified through medical records of their attending physicians. A positive history was defined as at least three episodes of middle ear problems during any single year between birth and 3 years. The CG had no history of middle ear disease during the 12 months prior to the collection of data. The medical records consisted of annual check-ups and visits scheduled by parents when they suspected an ear infection. It is acknowledged that the parents may not have always been able to recognize the presence of fluid buildup in the middle ears.

The NG consisted of children who had no more than one bout of ear disease in any single year

between birth and the time of the study, as verified by medical records.

PROCEDURE

Hearing and impedance screening was performed first to determine the child's eligibility to participate in the study. The hearing screening was performed at 10 dB hearing level for the frequencies 250, 500, 1,000, 2,000, and 4,000 Hz by means of the Grason-Stadler 1701 and Beltone model 110 audiometers. To decrease the possibility of extraneous auditory and visual distractions affecting the test results, the test administration took place in a sound-treated room. To control for experimenter bias, all testing was performed by individuals who did not know into which group each child was classified. To avoid test order effect, the order of presentation of each of the tests was randomized.

Auditory Perceptual Tests. The tape cassette version of the Goldman-Fristoe-Woodcock Sound Symbols Test Battery (GFW; subtests I to V) was administered individually. The volume of the tape was set at the most comfortable listening level as perceived by the subject. The subtests were administered in the following order: sound mimicry, sound recognition, sound analysis, sound blending, and sound-symbol association. Instructions to subjects were given before each test was administered.

Each of the five subtests on the GFW measured an aspect important to consider for language development. Sound mimicry measures the ability to imitate syllables received through the auditory modality. Sound recognition measures the ability to identify a familiar word when presented with a sequence of isolated phonemic components of that word. The child selects one of four pictures that corresponds to the combination of sounds. Subjects either "blend" the sounds to form the word and point to the correct picture, or they use a process of elimination by mentally discarding inappropriate pictures, depending on whether they are stronger as visual learners or as auditory learners. Some children would use a combination of both. Sound analysis measures the ability to identify phonemic components of syllables. The child listens to prerecorded nonsense syllables and repeats the first, last, or middle sound of each syllable, as requested. This test is very valuable for the reading teacher or speech-language pathologist in that it tells if a child is able to isolate phonemes within the words. The phonics method of teaching reading depends partially on this skill. The sound blending subtest measures the ability to blend sounds into familiar words. Many reading specialists believe that sound blending is a crucial skill underlying the ability

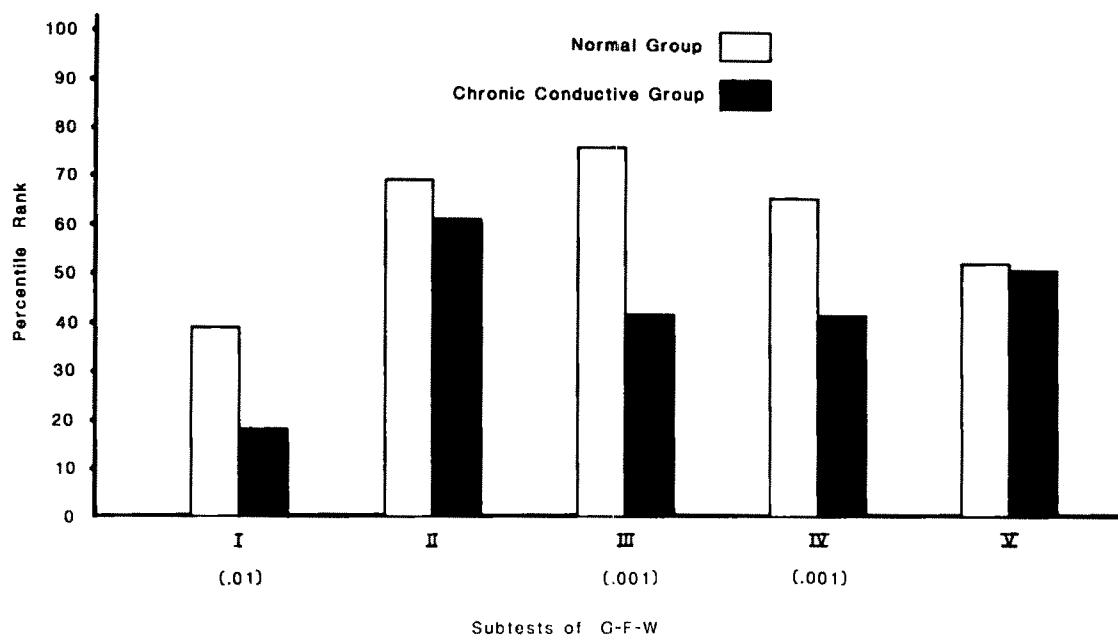


Fig 1. Mean scores in percentile rank for group with chronic conductive hearing loss versus normal-hearing group on Goldman-Fristoe-Woodcock (G-F-W).

to apply phonics skills to the identification of a word that is unfamiliar in print but part of one's receptive vocabulary.

Testing of sound-symbol association assesses the ability to learn new associations between unfamiliar auditory and visual stimuli. Pair-association learning of the type required for this test is a basic ability required in many academic learning tasks such as learning names of letters, learning sounds associated with single letters, learning spelling of nonphonetic words, and acquiring a sight-reading vocabulary. Each of these five tests was used to interpret effects on these learning tasks and styles by comparing the differences between the CG and the NG.

Peabody Picture Vocabulary Test. The PPVT (Revised form M) was administered individually. The standard score equivalent, percentile rank, and age equivalent for each child were recorded. No subjects were eliminated on the basis of low or high PPVT scores. The percentile rank was used as one of the

variables for pair-matching the subjects into the control and experimental groups.

Classroom Reading Inventory. The Classroom Reading Inventory (CRI) is designed to identify a student's specific word recognition and comprehension skills. This reading test was chosen since it evaluates specific reading skills: written word recognition, and comprehension of written and orally presented material. On the word recognition section of the CRI, the child is required to read graded word lists. The student's word recognition level is defined as the particular grade level at which the student mispronounces or does not know 5 of the 20 words. This information is used to estimate the approximate starting level at which the student will begin reading the graded oral paragraphs. The grade level referents for the CRI are preprimer, primer, and first, second, third, fourth, fifth, and sixth grades.

The CRI was administered individually. For each child, six scores were recorded: written word recog-

TABLE 1. ANALYSIS OF VARIANCE ON GOLDMAN-FRISTOE-WOODCOCK TEST RESULTS

Subtest	Source	df	Sum of Squares	Mean Squares	F Ratio	F Probability
I: Sound mimicry	Between groups	1	5334.0833	5334.0833	9.7922	.003
	Within groups	46	25057.5833	544.7301		
II: Sound recognition	Between groups	1	841.6875	841.6875	1.1682	.2854
	Within groups	46	33142.2917	720.4846		
III: Sound analysis	Between groups	1	14946.0208	14946.0208	20.0285	.0001
	Within groups	46	34326.9583	746.2382		
IV: Sound blending	Between groups	1	6816.3333	6816.3333	12.4943	.0009
	Within groups	46	25095.5833	545.5562		
V: Sound association	Between groups	1	28.5208	28.5208	0.0280	.8679
	Within groups	46	46924.7917	1020.1042		

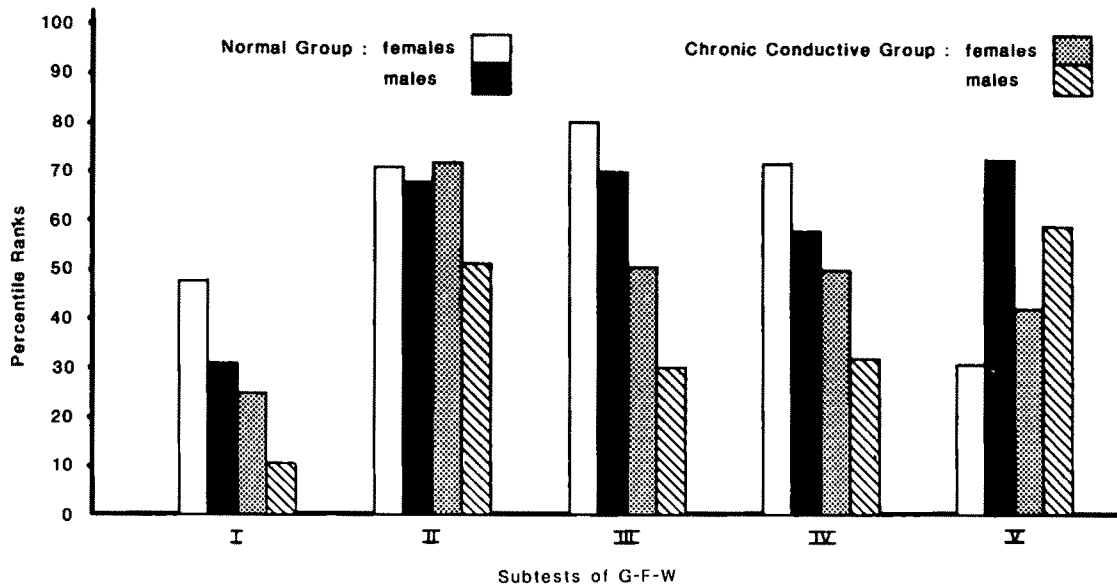


Fig 2. Mean percentile ranks of boys versus girls on Goldman-Fristoe-Woodcock (G-F-W).

dition (independent level, instructional level, and frustration level) and comprehension of written and orally presented material (independent level, instructional level, and frustration level). The CRI uses the Spache Readability Formula¹³ to determine the grade level of each group of words and paragraphs. This formula takes into account the vocabulary element of reading materials, sentence structure, complexity, and length. It is a criterion-referenced test rather than a norm-referenced test. It is recognized that grade levels do not present the best information statistically. However, it is important to determine how a child performs in reading at the independent, instructional, and frustration levels so that appropriate individualized instructional methods can be used.

RESULTS

Goldman-Fristoe-Woodcock Sound Symbols Test. Figure 1 presents the mean scores (in percentile rank) for each group on the first five subtests of the GFW. The NG performed better than the CG on all five tests of auditory perceptual skills. Analysis of variance (Table 1) indicates that there were significant differences in performance by the two groups on subtests I (sound mimicry), III (sound analysis), and IV (sound blending).

Figure 2 presents the performances of boys versus girls in each group on each of the five subtests of the GFW. Hotelling's multivariate test of significance of the effect of gender across groups yielded an F of 4.632, which was significant at the .002 level. The univariate F test of the effect of gender (Table 2) indicated that the girls performed significantly differently than the boys on GFW subtests I, III, IV, and V. Therefore, the girls performed significantly better than the boys on GFW I (sound mimicry), GFW III (sound analysis), and GFW IV (sound blending), while the boys performed better on GFW V (sound-symbol association). Hotelling's multivariate test of significance of the effect of group-by-gender interaction yielded an F of 0.794, which was not statistically significant. Therefore, there was no gender-by-group interaction.

Classroom Reading Inventory Form A. Figure 3 presents the mean scores of the NG versus the CG on the CRI. On each subtest, the NG outscored the CG. Analysis of variance (Table 3) indicates that the differences in performance between the two groups were statistically significant for each subtest. The NG therefore performed significantly better than the CG on all of the CRI subtests. For the NG, 42% of the children were reading at first-grade level for word

TABLE 2. UNIVARIATE F TEST ON EFFECT OF GENDER ON GOLDMAN-FRISTOE-WOODCOCK TEST PERFORMANCE

Variable	Error Sum of Squares	Error Mean Squares	F	Significance of F
Subtest I	22142.1667	503.23106	5.7908	.02
Subtest II	30707.2500	697.89205	2.16011	.149
Subtest III	31049.2500	705.66477	4.24071	.045
Subtest IV	22733.5000	516.67045	4.55222	.038
Subtest V	36333.5833	825.76326	10.89015	.002

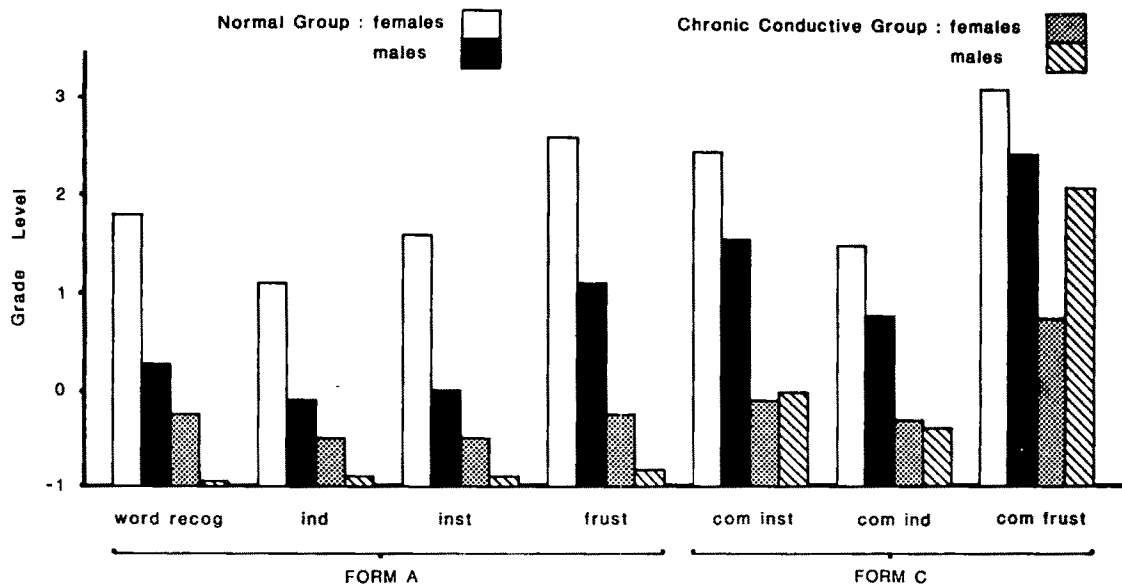


Fig 3. Mean scores of group with chronic conductive hearing loss versus normal-hearing group on Classroom Reading Inventory. Recog — recognition, ind — independent, inst — instructional, frust — frustration, com — comprehension.

recognition, while only 8% of the CG were reading at first-grade level. The reading grade level was determined by the CRI (preprimer, primer, and first and second grades), while grade level refers to the grade in which the child was enrolled. For comprehension of orally presented material, 71% of the NG were at first-grade reading level, while only 25% of the CG were performing at first-grade level.

The univariate F test of the effect of gender (Table 4) indicated that there were significant differences in performance between the boys and girls for both the control and experimental groups on each subtest of the CRI word recognition test. The girls therefore performed significantly better than the boys on word recognition at the independent, instructional, and

frustration levels. Hotelling's multivariate test of significance indicated that there was no significant interaction between group and gender. On word recognition, 12.5% of the NG boys and 29% of the NG girls were at grade level, while none of the CG boys and only 8% of the CG girls were at grade level.

Classroom Reading Inventory Form C. Analysis of variance (Table 3) indicated that the differences in performance of the NG versus the CG on each of the subtests of CRI form C were significant at the .001 level. Hotelling's multivariate test of significance of the effect of gender on the comprehension tests yielded an F of 2.83, which was significant at the .05 level. The girls and boys therefore performed significantly differently at all levels on the comprehension

TABLE 3. ANALYSIS OF VARIANCE ON CLASSROOM READING INVENTORY TEST RESULTS

Subtest	Source	df	Sum of Squares	Mean Squares	F Ratio	F Probability
A: Word decoding	Between groups	1	31.6875	31.6875	9.0653	.0042
	Within groups	46	160.7917	3.4955		
A: Independent level	Between groups	1	17.5208	17.5208	8.5324	.0054
	Within groups	46	94.4583	2.0534		
A: Instructional level	Between groups	1	28.5208	28.5208	9.9172	.0029
	Within groups	46	132.2917	2.8759		
A: Frustration level	Between groups	1	70.0833	70.0833	22.6102	.0000
	Within groups	46	142.5833	3.0996		
C: Comprehension independent level	Between groups	1	27.0000	27.0000	18.1978	.0001
	Within groups	46	68.2500	1.4837		
C: Comprehension instructional level	Between groups	1	65.3333	65.3333	31.5245	.0000
	Within groups	46	95.3333	2.0725		
C: Comprehension frustration level	Between groups	1	22.6875	22.6875	7.2579	.0098
	Within groups	46	143.7917	3.1259		

TABLE 4. UNIVARIATE TEST OF SIGNIFICANCE

Effect	Variable	Error Sum of Squares	Error Mean Squares	F	Significance of F
Of gender on performance on CRI	Word decoding	143.08333	3.25189	4.67036	.036
	Independent level	84.41667	1.91856	3.92004	.054
	Instructional level	114.58333	2.60417	5.00000	.030
	Frustration level	125.50000	3.85227	4.93758	.031
Of group on performance on subtest C	Independent level	64.8333	1.47348	18.32391	.000
	Instructional level	89.6667	2.03788	32.05948	.000
	Frustration level	129.7500	2.94886	7.69364	.008
Of gender on performance on subtest C	Independent level	64.8333	1.47348	1.41388	.241
	Instructional level	89.6667	2.03788	0.16357	.688
	Frustration level	129.7500	2.94886	0.34618	.559
Of group-by-gender interaction on performance on subtest C	Independent level	64.8333	1.47348	0.90488	.347
	Instructional level	89.6667	2.03788	2.61710	.113
	Frustration level	129.7500	2.94886	4.41554	.041

CRI — Classroom Reading Inventory.

tasks. The NG girls outperformed the NG boys on the comprehension skills at all levels, while the CG girls performed worse than the CG boys on the comprehension test at the instructional and frustration levels. The univariate F test of gender (Table 4) indicated no significant gender effect on the comprehension form. On comprehension of orally presented material, 37.5% of NG girls and 33% of NG boys were at grade level, while 12.5% of CG girls and boys were at grade level.

Intercorrelation of Tests. The Pearson correlation coefficients for the results on the PPVT and the five subtests of the GFW (Table 5) were calculated. Significant correlations were noted for the PPVT and GFW I to IV and among the first four subtests of the GFW. The GFW V (sound-symbol association) did not correlate significantly with the PPVT nor with any of the other sound-symbol subtests of the GFW.

The Pearson correlation coefficients were determined for the PPVT and the seven performance scores obtained on the CRI (Table 6). Significant correlations were obtained for the PPVT and the CRI form C: comprehension at the independent level. The seven levels of the CRI were significantly interrelated.

The Pearson correlation coefficients for each of the subtests of the GFW with each of the reading levels of the CRI were evaluated (Table 7). The GFW I to III were significantly correlated with each of the CRI reading levels. The GFW V had no significant correlation with any of the reading tests. The GFW II was significantly correlated with reading comprehension at the independent level only.

DISCUSSION AND CONCLUSIONS

The results of the present investigation suggest that chronic middle ear problems before the age of 3 years may have secondary effects that are evident later in life.

Auditory Perceptual Skills. The present study used children who did not have diagnosed speech-language problems. It is recognized that this restricted sample is a distinct subset of the chronic otitis media population in general. Nevertheless, the CG performed significantly worse than the NG on sound-symbol tasks involving only auditory symbols: sound recognition, sound mimicry, sound analysis, and sound blending. Of the four subtests, sound mimicry, sound analysis, and sound blending yielded the greatest between-group differences. The groups did not differ significantly in performance on sound-symbol tasks involving both auditory and visual symbols. It is hypothesized that the CG was able to use the visual symbol to help retain the auditory symbol and perform similarly to the NG on this task. Pair-association learning of the type required for this test is a basic ability in many academic learning tasks. The association of the visual stimuli may help to "fix" the auditory signal. Numerous studies of "cross-modal" learning suggest that there is a high correlation between reading skills and auditory-visual integration. Long-term memory storing is also used in the test. Early studies such as those by Birch and Belmont¹⁴ cite the importance of this cross-modal learning. Since great care was taken to pair-match the subjects in each group, with history of chronic otitis media being the single variable distinguishing the two groups,

TABLE 5. PEARSON CORRELATION COEFFICIENTS FOR PPVT AND CRI

	PPVT	CRI Word	CRI Ind	CRI Frst	Com Ind	Com Inst
CRI Word	-.01					
CRI Ind	-.00	.94*				
CRI Inst	.07	.95*	.95*			
CRI Frst	.13	.89*	.90*	.95*		
Com Ind	.40*	.68*	.71*	.73*	.76*	
Com Inst	.19	.63*	.64*	.66*	.68*	.84*
Com Frst	.23	.51*	.54*	.55*	.52*	.81*

PPVT — Peabody Picture Vocabulary Test, CRI — Classroom Reading Inventory, Word — word decoding, Ind — independent level, Frst — frustration level, Com — comprehension, Inst — instructional level.

*Significant at $p < .001$.

it is suggested that the CG children did not perform up to their potential on the auditory perceptual tests, owing to their early exposure to chronic otitis media and assumed auditory deprivation. These data agree with those of Brandes and Ehinger.⁶

The girls in both groups performed significantly better than the boys on auditory processing skills involving sound mimicry, sound analysis, and sound blending, while the boys in both groups performed significantly better than the girls on sound-symbol association tasks.

Reading Ability. The CG performed significantly more poorly than the NG on all subtests of reading skill: word recognition, comprehension of self-read materials, and comprehension of materials read to them. These results do not agree with those obtained by Brandes and Ehinger⁶ and Lous and Fiellau-Nikolajsen,¹² but do concur with other research that has found significant differences in reading ability.^{11,14}

Interrelationship of Auditory Perceptual Skills and Reading. The significant correlations (.001 level) of the receptive vocabulary (PPVT) with sound mimicry, sound recognition, sound analysis, and sound blending (GFW I to IV) demonstrate an interrelationship of these skills.

There were significant intercorrelations of the first

TABLE 6. PEARSON CORRELATION COEFFICIENTS FOR PPVT AND GFW

	PPVT	GFW I	GFW II	GFW III	GFW IV	GFW V
GFW 1	.46*					
GFW 2	.60*	.49*				
GFW 3	.47*	.47*	.53*			
GFW 4	.46*	.53*	.59*	.65*		
GFW 5	.10	.07	.08	-.12	.03	

PPVT — Peabody Picture Vocabulary Test, GFW — Goldman-Fristoe-Woodcock, I-V — subtests (see text).

*Significant at $p < .001$.

TABLE 7. PEARSON CORRELATION COEFFICIENTS FOR GFW AND CRI

	GFW I	GFW II	GFW III	GFW IV	GFW V
CRI Word	.26*	.22	.46*	.41*	-.11
CRI Ind	.33*	.19	.45*	.39*	-.16
CRI Inst	.33*	.22	.46*	.40*	-.10
CRI Frst	.39*	.23	.55*	.42*	-.11
Com Ind	.51*	.39*	.63*	.62*	-.01
Com Inst	.36*	.18	.55*	.53*	-.09
Com Frst	.23*	.20	.41*	.38*	.03

See Tables 5 and 6 for abbreviations.

*Significant at $p < .01$.

four subtests of the GFW, indicating that sound mimicry, sound recognition, sound analysis, and sound blending are all auditory perceptual skills that are highly intercorrelated. However, the correlations were not strong, ranging from .47 to .65. There was no significant correlation of GFW V (sound-symbol association) with any of the other GFW subtests. The added unfamiliar visual symbols change the type of skill needed.

There was a significant correlation of receptive vocabulary (PPVT) with the comprehension of auditory material (comprehension at the independent, instructional, and frustration levels). There was no significant correlation of receptive vocabulary skill and word recognition, as evaluated by the child's ability to sound out written words. These data point out that the ability to process meaningful auditory material is very much related to receptive vocabulary skills, but that the ability to recognize written words is an entirely different kind of task that is not necessarily dependent on a rich receptive vocabulary.

There were significant correlations among the various levels of the CRI. This suggests that the skills essential to recognizing and comprehending written words or sentences are similar to those required for the comprehension of auditory materials.

There were significant correlations among the GFW I, III, and IV and all levels of the CRI. This indicates a relationship among the auditory perceptual skills of sound mimicry, sound analysis, and sound blending and word recognition and reading comprehension. These results support those of earlier research.^{14,15} The absence of a significant correlation of the GFW V with any level of the CRI reading tests points to the possibility that the skills required to perform well on the sound-symbol test of the GFW have very little relation to those required for reading and comprehending meaningful written material.

IMPLICATIONS

While great care was taken to ensure that none of

the children who participated in this study had diagnosed language or articulation problems, it is possible that some or all of the CG children had subtle oral language deficits involving knowledge of syntax, spelling, and pragmatic skills. By deliberately limiting the subjects of this study to those with normal speech and language skills and no learning disabilities, the authors were aware that a specific subgroup had been targeted for the initial research. An assessment of the complex and subtle facets of oral language in the CG may yield further information regarding the language skills of children with histories of chronic ear infections. Follow-up studies are already in progress adding a third population of children in the same age range: children with diagnosed speech and language problems and children with documented learning disabilities. These studies should help to complete this picture.

From the results of this study, it can be interpreted that chronic ear infections during the critical early years of language development may affect the development of auditory perceptual and reading skills even in children who do not experience any speech-

language development problems. The possibility of long-term detrimental effects of early-onset chronic otitis media on auditory perceptual abilities and reading skills warrants investigation. Follow-up studies using the same children in 4 years' time may reveal whether the differences in abilities apparent at an early age persist.

Recurrent middle ear disease in young children should be regarded not only as a medical problem, but also as a potential education hazard for young beginning readers. Downs et al¹⁶ and Garrard and Clark¹⁷ have proposed educational alternatives for otitis-prone children concurrent with ongoing medical treatment. Such programs encourage parents to provide a language-rich environment for their children. The use of such programs involving intensive auditory stimulation may help to prevent long-term auditory learning problems in children who have recurrent otitis media. Early identification, aggressive medical treatment, and active language stimulation all have an essential role to play in minimizing the possibility of auditory perceptual deficits and reading problems in young children.

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IMAGING CASE STUDY OF THE MONTH

ROUNDED ATELECTASIS

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INTRODUCTION

Rounded atelectasis (RA) is a radiographic finding not previously discussed in the otolaryngology literature. Its chest x-ray appearance is often characteristic, but differentiation from neoplasm is sometimes difficult. The finding may present itself in both the routine evaluation of patients and in the metastatic workup for head and neck cancer. It should therefore be recognized by the head and neck radiologist and surgeon. We present two cases diagnosed radiographically, with a discussion of the entity.

CASE REPORTS

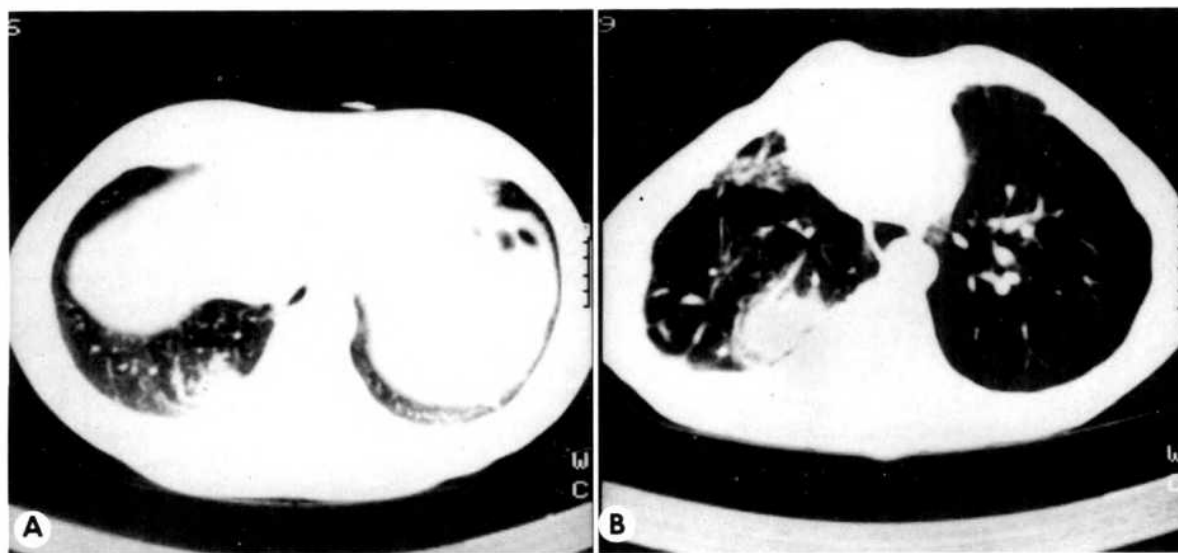
Case 1. A 63-year-old man presented with increasing dyspnea. He underwent urgent tracheotomy. Endoscopy revealed a T4N1M0 transglottic squamous cell carcinoma. The preoperative and metastatic workup included a chest x-ray study and thoracic computed tomography (CT). They demonstrated pleural disease consistent with asbestos exposure, and a right lower lobe density abutting the pleura. The patient underwent induction chemotherapy followed by modified neck dissection and then concomitant chemotherapy and irradiation. The right lower lobe density has not changed over 7

months. It is consistent with RA.

Case 2. A 53-year-old man had a history of cigarette smoking and 30 years of working with asbestos. He developed a T4N0M0 transglottic squamous cell carcinoma. Computed tomographic scans revealed multiple calcified and uncalcified pleural plaques and a 4-cm right lower lobe mass abutting the pleura and consistent with RA. Following wide field laryngectomy in May 1988, the patient developed a neck recurrence in January 1989. He has undergone resection of the neck recurrence. The RA has not changed.

DISCUSSION

First described in 1966 as "folded lung" by Blesovsky,¹ RA has since been referred to as atelectatic pseudotumor,² shrinking pleuritis with atelectasis,³ and pleuroma. More recently, the term RA has been accepted. The two principal radiographic features are 1) a round or oval mass usually no more than 5 cm in diameter that is peripheral in the lung and connected to the pleura at the point of greatest pleural thickening and 2) curving vessels and bronchi that enter the lesion and give a characteristic "comet" sign on plain films and linear tomography, and a "talon" sign (see Figure) on CT.⁴⁻⁶ The vessels



Computed tomograms showing rounded atelectasis with oval mass adjacent to pleura and appearance of "talon" or hawk's foot. A) Case 1. B) Case 2.

and bronchi enter the mass from below. Other findings include depression of the lung root, ipsilateral mediastinal shift, and overdistention of the opposite lung. The mass is usually found in the lower lobes. Computed tomographic scans may be useful when plain films are not diagnostic.

Many cases of RA have undergone exploration, and some have been resected. Gross pathologic findings consist of a coating of several layers of fibrous tissue causing folding and atelectasis of the underlying lung tissue. Following removal of the coating, the atelectatic lung can nearly always be reexpanded.

The cause of RA is controversial. Most authors agree that irritants such as asbestos or cigarette smoke cause a localized pleural reaction. This leads to formation of a thickened fibrotic coating over a limited area of lung. The coating shrinks, causing folding of the underlying parenchyma with atelectasis. Fibrous septae that extend into the parenchyma

also shrink and further contribute to the balled-up appearance.³ A second theory implicates compression of the parenchyma by a pulmonary effusion leading to folding of the lung.⁷

Treatment is unnecessary when the radiographic findings are diagnostic.⁸ Rounded atelectasis causes too little interference with lung function to justify operation. Fine needle aspiration is not routinely useful. These lesions may be followed serially, and it has been proposed that their radiographic characteristics be accepted among the criteria for benign intrathoracic masses.

CONCLUSION

Rounded atelectasis is a clinical entity that may mimic malignancy. Its association with pulmonary irritants links it with head and neck cancer patients. Recognition of its benign nature dictates a conservative approach of nonintervention and serial CT scans to follow its progress.

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PATHOLOGY CONSULTATION

EPITHELIAL-MYOEPITHELIAL CARCINOMA OF SALIVARY GLANDS

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Epithelial-myoepithelial carcinomas comprise approximately 1% of all salivary gland neoplasms. They are preponderantly tumors of the parotid glands with a relatively low mortality but a decided locoregional aggressiveness. Histopathologically, the carcinomas are characterized by a dual cell population of epithelial (ductal) cells and myoepithelial cells. These cells vary in their dominance and phenotypic expression.

Establishment of epithelial-myoepithelial (epimyoepithelial) carcinoma of the salivary glands as a diagnostic entity is another example of evolutionary change in the classification of salivary gland neoplasms. The neoplasm was not listed in the 1972 World Health Organization (WHO) classification,¹ but was illustrated in the WHO publication on histopathologic typing of salivary gland tumors with the caption of "clear cell monomorphic adenoma." In the 1991 (second edition) WHO publication,² epithelial-myoepithelial carcinoma receives its rightful recognition and, in the event, "clear cell monomorphic adenoma" is deleted. This change in taxonomic status is the outcome of clinicopathologic investigations (see Table³⁻⁶) that also recognize the preponderantly parotid carcinoma as accounting for slightly fewer

than 1% of all salivary gland neoplasms.³⁻⁸

Befitting a neoplasm composed of epithelial- and myoepithelial-differentiated cells, this salivary carcinoma is capable of a spectrum of histopathologic appearances. The classic bicellular form is unmistakable with hematoxylin and eosin stains and light microscopy (Fig 1A,B). It has an almost pathognomonic low-magnification growth pattern: lobular, pushing invasion; a coagulative necrosis in the center of lobules (Fig 1C); occasional encephaloid protrusions into cystic spaces (Fig 1D); and a variably expressed circumscription (at times encapsulated). The cellular constituents are arrayed in a mucoid or mucohyaline stroma in the form of ducts (with or without inspissated secretions) surrounded by a mantle of cells with optically clear cytoplasm. The ductal cells usually have a banal, intercalated duct appearance, and their size is subordinate to the larger outer layer of clear cells (Fig 1A,B). By location and phenotypic expression, these mantle cells are myoepithelial. The optically clear cytoplasm nearly always contains glycogen, and never mucin. By immunostaining, the myoepithelial cells show S-100 protein antigen (Fig 2A) and/or smooth muscle actin reactivity. In contrast to the less conspicuous inner ductal cells, there is no keratin immunoreactivity in the mantle cells. Nuclear pleomorphism and a high mitotic rate are not seen.

Electron microscopy confirms the hematoxylin and eosin and immunostaining determinations of two sorts of cells: the duct cells have electron optic features of intercalated duct cells, and the clear cells are myoepithelial with abundant glycogen and myofilaments.²

The blunt, lobular growth and the stroma of the

EPIMYOEPITHELIAL CARCINOMA OF SALIVARY GLANDS

	No.	%
Patients	67	
Male	25	37
Female	42	63
Salivary gland site		
Parotid	52	77
Submandibular	7	10
"Minor salivary glands"	4	
Buccal mucosa	1	
Maxillary sinus	1	
Not stated	2	
Patients with recurrences	21	31.3
Patients with cervical lymph node metastases	12	17.9
Patients with distant metastases	5	7.5
Patient deaths attributed to neoplasm	5	7.5

Compiled from data in references 3 through 6. Mean age at diagnosis was 62 years (range, 27 to 83).

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

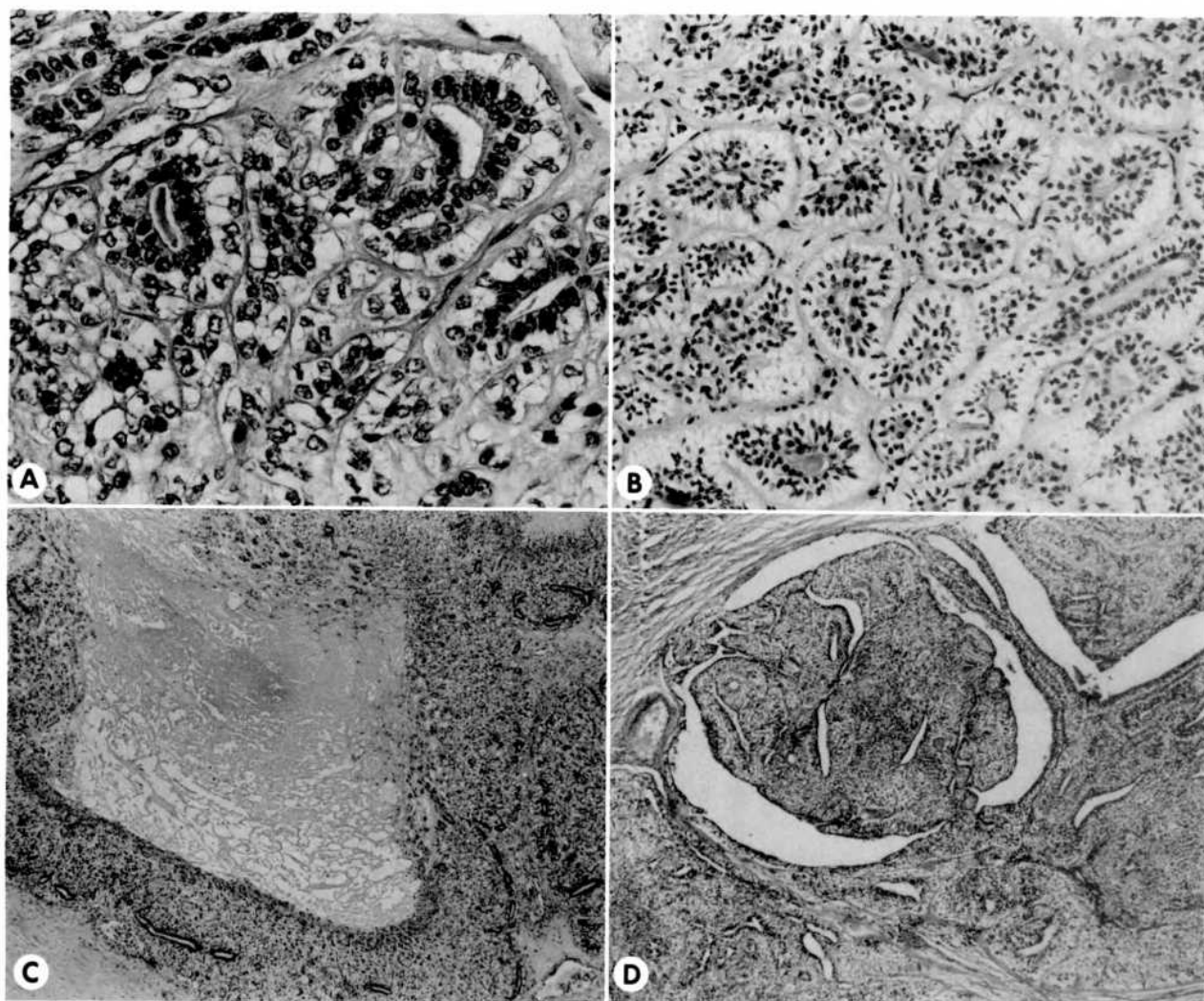


Fig 1. Epithelial-myoepithelial carcinoma of parotid gland. A) In its classic biphasic appearance with clear myoepithelial cells surrounding, in mantle form, small ducts (H & E, original x240). B) With striking dominance of myoepithelial clear cell component (H & E, original x140). C) Blunt, lobular growth with central coagulative necrosis — common feature (H & E, original x45). D) Intraductal polypoid projection (H & E, original x60).

carcinomas are quite constant, but the ratio of epithelial- to myoepithelial-differentiated cells accounts for the different expressions manifested by the carcinoma. These consist of 1) a preponderance of clear cell constituents and a paucity of epithelial-lined ducts and ductules (Fig 2B), 2) spindle myoepithelial forms (Fig 2C), and 3) an exaggerated and less benign appearance of the ductal epithelium (Fig 2D). These variations can be found in areas of an otherwise classic epithelial-myoepithelial carcinoma, or they can be the dominant features.

The paravascular clear cell variant poses the differential diagnosis of a mucoepidermoid carcinoma. Negative mucin stains usually dispel that alternative. Less readily excluded is the clear cell neoplasm that exhibits no biphasic areas and no electron optic or immunocytochemical markers of myoepithelial differentiation. It is not mucin-forming, nor is it usually glycogen-rich. Judged by our experience and the few

cases reported in the literature, this unusual to rare carcinoma is exclusively an intraoral neoplasm and of a low-grade malignant potential.⁹

As the data in the Table indicate, the clinical behavior of epimyoeplithelial carcinomas is that of a relatively low-grade malignancy with a primary locoregional aggressiveness. It nevertheless can be lethal.

Analogous lesions occur in the breast and more rarely arise from adnexae of the skin. In the breast, the lesions have been divided into myoeplitheliosis, adenomyoeplithelioma, and myoeplithelial carcinoma.¹⁰ The reported descriptions and photomicrographs of the first two are identical to those of epithelial-myoeplithelial carcinoma of salivary glands. Myoeplitheliosis is considered to be a benign lesion. Mammary adenomyoeplitheliomas have a potential for local recurrence, but none is known to have metastasized.¹⁰

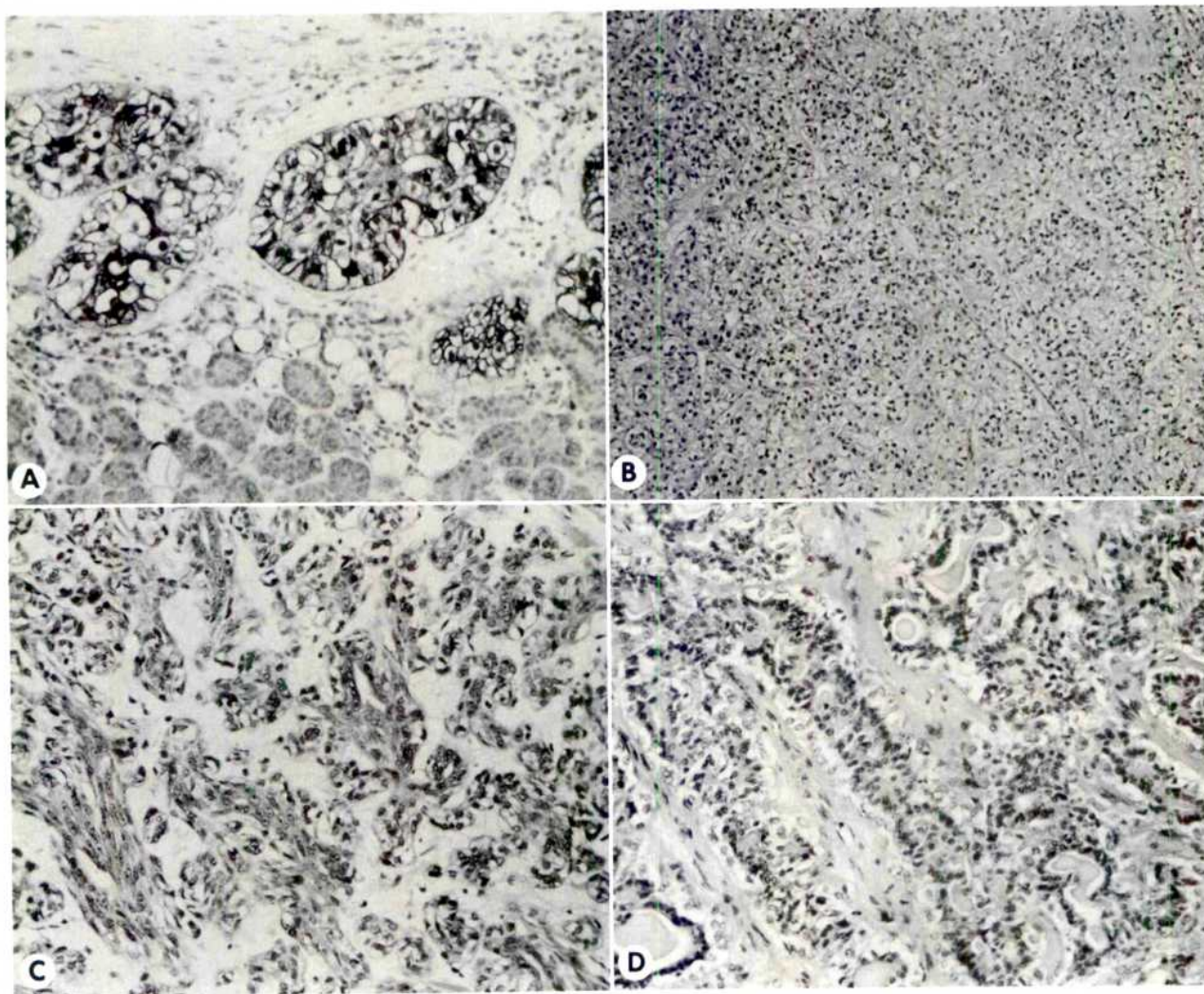


Fig 2. Epithelial-myoepithelial carcinoma. A) Of parotid gland, showing positive immunostaining for S-100 protein antigen in clear cells of lobules (original x160). B) Of parotid gland, manifesting, in this field, only its clear (myoepithelial) cell component (H & E, original x45). C) Of parotid gland, showing small, inconspicuous ducts and spindle myoepithelial cells as dominant features (H & E, original x140). D) Of maxillary sinus (H & E, original x200). In this unusual site, there is ductal epithelial prominence.

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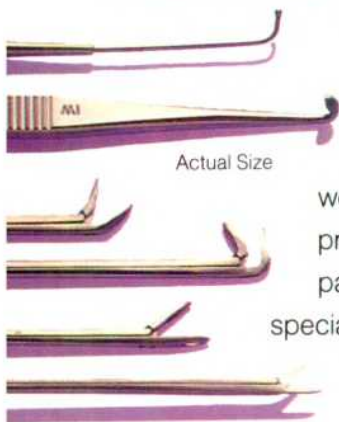
*Concha bullosa on left side bulging into lateral nasal wall. Entrance to middle meatus blocked and a polyp is arising from the contact area.**

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ANNALS OF HEAD & NECK MEDICINE & SURGERY®

VOLUME 101

JULY 1992

NUMBER 7

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EDITORIAL

ARE WE READY FOR THE YEAR 2001?

Are we ready for the year 2001? I wonder. The biggest problem in medicine today — and this is just as true in our specialty as any — is not diagnosis and treatment, but economics.

Our diagnostics have improved dramatically in just the last decade. In our specialty alone we have benefited greatly: electronystagmography, magnetic resonance imaging, and position emission tomography, in which we can actually see the physiology of the brain in terms of glucose and oxygen metabolism.

In therapeutics, we have come to the era in which skull base surgery is almost solely the province of the otologist-neurotologist and probably 80% of acoustics are done by them (a figure unheard-of in the 1960s), cochlear electrode implant is commonplace and unexpectedly successful in adults as well as children (even pre-linguals), and phonosurgery has replaced Teflon vocal cord injection with superior results. It is also clear we have moved into the era of immunotherapy of squamous cell cancer of the head and neck. The infusion of lymphocytes drawn from the patient and sensitized to the tumor cells has in a number of centers around the world resulted in dramatic reduction of inoperable cancers and, especially in combination with chemotherapy, resolution. This alone is very exciting.

Those are some of the good things, among many others, that are bound to continue and improve into the next century. I would be less than candid, however, if I failed to report to you my concerns about the controls on medical expenditures, and the probable state of affairs in 2001.

First of all, it is clear our society cannot continue to pour into health care of our citizens an amount now approaching 15% of our GNP. No other Western country in the world comes near this. Alternatives to our system have been suggested. There has been in the newspapers of this country what seems to be a yen for the Canadian system. How good is it? Stephen Chapman, a noted columnist, reported some very interesting data in a column 4 months ago entitled "National Health Insurance: Does It Work Abroad?"

This is what he states:

Most Americans know less about the Canadian health-care system than they do about the Canadian Football League, but one poll found that 66 percent would trade for it sight unseen.

That may be the best way to do it, since looking closely can spoil all the fun. Spoiling the fun, however, is the occasional duty of public policy organizations like the Dallas-based National Center for Policy Analysis. It has published an indispensable report entitled "Twenty Myths About National Health Insurance," written by its president, John C. Goodman, and Gerald Musgrave, a former Stanford economist. Their investigation is a cold shower for anyone attracted to the sort of health-care systems operating elsewhere.

Chapman quotes a whole series of misconceptions of health care and costs in America as identified by Goodman. It is useful to consider them individually.

Take a myth, any myth.

Other countries spend less on health care? Most of the difference stems from the fact that the U.S. is wealthier than most countries and that as people grow more affluent they devote a bigger share of their spending to health care.

Our costs are soaring out of control? During the 1980's, Goodman and Musgrave found, health-care spending rose faster in 11 of 15 advanced countries than in the United States. Among those who did worse than we did were such health-care models as Canada, Britain and Germany.

The health of Americans is worse than that of other Westerners? There's some truth here, but the reasons have little to do with medicine — crime, poverty, teen pregnancy and assorted unhealthy habits. Where medical treatment can make a difference, though, the U.S. does very well.

For premature babies, for children born with spina bifida or for people who have cancer, a brain tumor, heart disease or chronic renal failure, says the report, the chances of survival are best in the U.S. The U.S. treats more people for kidney failure, as a percentage of its population, than any other Western country. It installs 20 times more heart pacemakers per capita than Canada.

Goodman and Musgrave (quoted by Chapman) make a telling point in the following, which clearly amounts to rationing of health care in surgical relief of disease which doesn't exist in America.

Other countries may proclaim a general right to health care, but their citizens often find that they don't have a right to anything specific. If you need heart bypass surgery in Canada, you may wait five months. For a cataract operation, a year. Britain has more than a million people waiting for surgery. In both places it's not unusual for people to die waiting for the operation that would save them.

Since old people need the most medical care, you might think they would gain the most from national health insurance. In fact, they tend to be the ones who get shafted. The U.S. performs twice as many heart bypass operations as Canada — but four times as many for people aged 75 or older. If you're over 65 in Britain and need kidney dialysis, you'd better draft a will.

In fact, if you're old and not perfectly healthy, the U.S. is among the best places to be. Medical care is only a minor factor in the life expectancy of young people, but it's a major one for old people. In life expectancy for 80-year-old males, the U.S. is second among the advanced nations, behind Iceland; for women, it trails only Iceland and Canada.

The US system is supposed to be singularly cruel to the destitute, but Goodman and Musgrave amass considerable evidence that in countries *with* national health insurance, politicians cater to the *middle* class. "In general," they write, "low-income people in almost every country see physicians less often, spend less time with them, enter the hospital less often and spend less time there" than those who are not poor.

Goodman and Musgrave sharpen their viewpoint:

Our system, despite its shortcomings, does ensure that the poor get in the hospital door, through Medicaid and public hospitals. Once inside, they benefit from the most advanced medical care in the world — of the sort that even well-to-do patients in places like Britain are routinely denied.

Goodman and Musgrave make it plain that the main reason foreign health-care systems look so good is that they're so far away. The US system can stand some improvements, but anyone who thinks national health insurance would improve it is likely to get a surprise.

So it appears, through the eyes of Chapman and his careful analysis of the work of Goodman and Musgrave, that neither the Canadian or English health care plans would be an improvement over what we have.

In this election year, Bush, all other presidential hopefuls, many senators and representatives, and dozens of medical associations, hospital groups, and think tanks are proffering their health care plan. Joan Beck, a columnist whose work I have thought to be balanced and objective in terms of health affairs, made these points in a column 5 months ago.

A national consensus is building that major changes must be made in our disjointed, expensive, unfair jerry-built system of health care. But there is little agreement on whose plan should be tried, how a new system should be structured — and especially — who will get stuck with the bills.

In sorting through the campaign hyperbole, the self-interested slogans and the do-gooder wishful thinking, voters and taxpayers should resist signing on to any plan until they have satisfactory answers to critical concerns. A sampling of them:

If a proposal calls for a single national health-care system run by the federal government, what assurances will we have that it will work efficiently, caringly and cost-effectively?

This is the same federal government that gave us IRS regulations, \$600 Defense Department toilet seats and a national debt approaching \$4 trillion. It's the same government that couldn't or wouldn't stop the savings-and-loan debacle or collect on the lunch chits of members of Congress.

Where would the money come from? Higher tax rates, jeopardizing consumer spending? Taxes on employers, hampering economic growth and job creating? A special employer-employee payroll tax such as Social Security? More deficit spending? Is it *logical* to assume that a combination of price controls, which historically have had disastrous side effects, and bureaucratic decision-making can be *trusted* with such life-and-death matters as health?

Who will pay for the free or low-cost health care to be provided for the estimated 31 million to 37 million people who have no insurance?

In what are called "play or pay" plans, employers would be required to buy basic health coverage for all employees or pay a per-capita charge into a fund to provide for all the uninsured. No one knows how steep such "play or pay" payments would become if health-care costs keep rising. Or whether employers who are hurting because of health insurance bills would have to pay still more. Or how many small businesses simply would dump their workers onto the government fund. Or what tax sources would be used to enable the fund to pay for all the uninsured?

Will incentives built into a national health-care plan to hold costs down jeopardize patients' care? Medicaid has held down payments to hospitals so sharply some have had to close. Medicaid fees for physicians are so low some doctors refuse poor patients or run "Medicaid Mills." Medicare payments to hospitals have forced the discharge of some patients before it was in their best interest.

If a plan calls for "a basic level of care for everyone," what won't be covered? This phrase often is used as a code for rationing. It usually means the proposal won't cover certain conditions such as infertility or transplants or that it has age limits or other restrictions.

Some kinds of rationing may seem necessary if costs can't be controlled, or may even seem preferable to the tacit rationing of long waits for care under some national-health systems. But the public should understand how such a plan intends to shave costs.

If a proposal covers long-term nursing-home care, does it include reasonable estimates of the cost? Millions of disabled elderly are cared for by their families, often with great difficulties, because they can't afford bills for nursing-home care. No one knows how many of these people would be shifted to nursing homes if a national health-care plan paid the bills. A federal program qualifying homes to admit them would sink the whole program, especially in view of the worsening of the problem as our population inevitably ages as we prolong life. And each time Congress takes a stab at relieving the burden of nursing-home costs, it gives up in dismay.

Finally, consider the fact that the annual cost of health care for osteoporosis alone amounts to \$10 billion (fractures of the hip number 250,000, spine 500,000, wrist 170,000). Included in this figure is the 18% that will have to enter a long-term institution. This figure will grow of course, as our aged population grows (NIH, Jan 1992).

With all of the above, I have not even mentioned the growing encroachment of physician time in carrying out the paperwork of quality assurance documentation (which means this is what I did here-there-and-when, and sign for it). And also studying code numbers for types of "visitations" (office or hospital, intensity-graded) of which there are over 50! This, in order to be justly paid for what was automatic a few years ago. One wonders how much better care our patients would receive if we spent these hours in journal reading and postgraduate exercises!

I don't know if I have answered the question cited, "Are we ready for the year 2001?" I do think we are ready if we come to grips with the medical problems discussed here and are allowed to do so. But I do not think the executive or legislative branches of government are; there is much disarray. The only thing we can do about this is through the ballot box, and personal pressure upon our congressmen.

Let me cite the economic scenario which disturbs me the most at the moment. Medicare as of March 1st pays \$1,122 in Iowa for a laryngectomy (and as little as \$710 in some states). Our charge is \$3,300. They pay against our charge for a myringoplasty (eardrum rebuilding) \$540; our charge, and we believe it just, fair, and reasonable, is \$2,080. Thus Medicare now pays between a third and a quarter of what it costs us to pay our bills and make a reasonable profit. But, one shoe has dropped. Now, if the Blues follow, the other shoe drops, and the commercial insurers will scramble to follow suit. If that happens, we are *out of business*. We can't *exist* with only a third or half of our prior revenue. If the Blues announce such a plan, each state medical society should organize relentless pressure against it.

What is the solution? I cannot here offer one. What I do know is that any solution to a difficult problem must be preceded by a logical and calculated analysis of the problem, with a clear view of alternatives. This is what I have tried to offer here.

Brian F. McCabe, MD
Editor

*This article originally appeared in March 1937, Volume 46, No. 1, pages 3-12,
and is reproduced here in its entirety.*

ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY

VOL. 46

MARCH, 1937

No. 1

THE SURGERY OF OTOSCLEROSIS*

PROFESSOR GUNNAR HOLMGREN

STOCKHOLM, SWEDEN

For the diminution of hearing in otosclerosis there is no generally accepted remedy, chiefly because of the fact that hitherto none of the various procedures have produced demonstrable results. Surgical methods may be considered an exception to this rule in as much as every operator who has sought to solve the problem has obtained immediate and noticeable improvement in hearing as soon as a fistula was produced leading to the labyrinth, in different locations.

This occurred for the first time as Kessel, in 1876, removed the stapes in order to replace the footplate with a (movable) scar membrane. Passow obtained the same result in 1897 by trephining the promontory. In these cases improvement in hearing was not permanent but lasted only a few days.

The opposition to these experiments was strong and quite universal. At the Congress in Rome, in 1894, leading otologists (Politzer, Moure and Cozzolino) condemned stapes extraction as useless and dangerous. At the Congress in Paris, in 1900, Siebenmann and Botey took exception to the method as ineffectual, dangerous to hearing and to life, and essentially futile in view of the nature of the disease. An equally adverse stand was taken by Denker, in 1904, in his monograph, "Otosclerosis."

*Read before the III International Congress of Oto-Rhino-Laryngology at Berlin, August, 1936.

A decade passed before the question was again taken up, this time by Bárány. Supported by his well-known theory of the function of artificial ear drums, Bárány suggested a fistula into the posterior vertical canal through which better hearing might be established and aseptic conditions maintained. Both aims were accomplished, but the results persisted only a few days.

In 1913 Jenkins opened the horizontal semicircular canal in two cases. He covered the fistula in one case with a Thiersch graft, in the other with a flap from the external meatus, and obtained in both cases an undoubted improvement in hearing. One patient became completely deaf soon thereafter and the other so nearly so that Jenkins abandoned the method.

With a view to bringing about a more lasting result by covering the fistula at operation with an elastic membrane, thus producing primary healing, Holmgren in 1917 suggested making the fistula at the upper part of the anterior vertical canal, removing the bone between the dura and the fistula and thus bringing about primary healing between the two. In one case operated upon by this method, the immediate hearing result was good but of short duration. A proposal by the same author to produce a still thinner scar through excision of the dura over the fistula with primary union with the arachnoid was not attempted.

Somewhat later, Bárány suggested a new technic in two stages. In the first the processus mastoideus was opened with gouges and the hollow was filled with fat. Some weeks later, at a second sitting, the horizontal semicircular canal was trephined and a small morsel of fat brought in apposition to the fistula to keep it open. The effect on the hearing was satisfactory but lasted only two weeks.

In 1920, Holmgren suggested a new technic to the Oto-Rhino-Laryngological Congress in Paris. This operation was carried out under magnifying instruments (Gullstrand's loop and Zeiss' binocular microscope). The fistula, originally established at the promontory, was covered with mucoperiosteum previously turned to one side. This method gave good but only temporary results.

Two years later, Holmgren attempted a fistula into the horizontal semicircular canal, which he covered immediately with the mucoperiosteum of the ampulla. This time the hearing was much improved and it was only after a few weeks that it again disappeared. In several cases, however, the improvement, though not great, was lasting. By this method, which could point to some results, however

THE SURGERY OF OTOSCLEROSIS

small, otologic patients with increased bone conduction were operated upon with the result that they were able to resume occupations which they had been forced to abandon; in all, some thirty-five in a period of fifteen years. It was observed by some of these patients that hearing in the unoperated ear became progressively worse but in the ear operated upon remained stationary. The worse of the two ears was therefore operated upon, which is now in many cases the better one. Sourdille observed and published such a case.

I shall not dwell upon Wittmaack's and Heyninx's well-known operations, as these do not anticipate an improvement in hearing but only an arrest of symptoms.

Since 1924, Sourdille attacked the problem with a unique intelligence and technical facility. I shall not enter into a discussion of his technic nor his results, as he is appearing personally before this Congress. His experience now embraces numbers of cases which, albeit after repeated tedious and technically difficult operations, have attained undeniable and enduring improvement. Stimulated by the optimism engendered by Sourdille's results, I have recently reopened the problem.

Since my patients formerly operated upon obtained a good—in fact, of late a very good—primary hearing, although the end results were minute, I assume that this was due to the fact that not merely a fibrous but a bony covering of the fistula had occurred. I attempted to cover the fistula according to Thiersch, a method formerly suggested by Floderus, later by Jenkins, possibly by others. One of these patients has had for many years an undoubted improvement which is not great but sufficient to permit him to resume his former occupation which before the operation he had had to abandon. This method had the disadvantage that the patient retained behind his ear a permanent opening lined with squamous epithelium, which now and again required attention. Therefore, I abandoned the method.

The method which I have finally evolved has now given considerably better results over a period of one and one-half years. Before I describe this more closely I wish to present several cases.

REPORT OF CASES

CASE 1.—E. K., 50-year-old teacher, Kiruna. Examined in 1928, 1935 and 1936. One brother and two cousins are deaf. There has been a progressive diminution of hearing on both sides, for the past thirty years on the left, seventeen on the right, with paracusis Willisii and intermittent tinnitus. The drums are irregularly thickened, somewhat retracted after otitis at the age of 17. Fixed. X-ray shows normal pneumatization except at the apex.

GUNNAR HOLMGREN

6. 5, 1936.—Hearing test.

Right		Left
0	Whisper	ad concham
0.2 meter	Conversation	1 metre
C128	Lower limit	C128
5 seconds	C128 air conduction	15 sec. (normally 120)
45 seconds	C128 bone conduction	45—50 sec. (normally 45)

6. 6, 1936.—Operation for otosclerosis on right ear, in which the reduction of hearing had reached the highest degree and the progression was going on most rapidly. Healing per primam. Length of stay in hospital, eleven days.

7. 14, 1936.—Hearing test. Right ear.

Whisper	0.15 meter
Conversation	10 meters
Lower limit	C64
C128 air conduction	33 seconds (normally 120)
C128 bone conduction	75 seconds (normally 45)

The patient was operated on because of the progressive reduction of hearing, which threatened to keep her away from her work.

CASE 2.—A. D., age 33, woman farm laborer, Fränsta, Central Sweden. Examined April-June, 1936.

Heredity uncertain. Progressive reduction of hearing for six years in the right, for two years in the left ear. Treated without effect, lately with thyroxin.

Nervous patient operated on for Basedow's disease.

Normal position and normal mobility of the tympanic membranes. X-ray, normal pneumatization, no pneumatization of apex.

5. 14, 1936.—Hearing test.

Right		Left
0	Whisper	0.3 meter
0.5 meter	Conversation	2.5—3 meters
C128	Lower limit of tone	C64
3 seconds	C128 air conduction	20 sec. (normally 120)
45 seconds	C128 bone conduction	45—50 sec. (normally 45)

5. 15, 1936.—Operation for otosclerosis in the right ear, in which the reduction of hearing had reached the highest degree. Healing per primam. Length of stay in hospital, 28 days.

7. 14, 1936.—Hearing test. Right ear.

0.15 meter	Whisper
10 meters	Conversation
C64	Lower limit of tone
40 seconds (normally 120)	C128 air conduction
65 seconds (normally 45)	C128 bone conduction

The comparatively long stay in hospital was in this case due to the lability of the nervous system of the patient.

THE SURGERY OF OTOSCLEROSIS

CASE 3.—K. K., age 50, foreman, stone cutter, Stockholm. No hereditary otosclerosis. Bilateral progressive reduction of hearing for thirteen years. Singing in his ears like the sound of a waterfall, feeling of intense heaviness in his head. Tympanic membranes somewhat thickened. X-ray: Normal pneumatization, no pneumatization of the apex.

10. 10-22, 1935.—Hearing test.

Right		Left
0	Whisper	0
0.20 meter	Conversation	0.50—1 meter
C256	Lower limit of tone	C128
0	C128 air conduction	
65 seconds	C128 bone conduction	65 sec. (normally 45)

10. 22, 1935.—Operation for otosclerosis. The operation was carried out on the right ear, in which the reduction of hearing was most pronounced.

6. 8, 1936.—Hearing test. Right ear.

0.20 meter	Whisper
4 meters	Conversation
C256	Lower limit of tone
0	C128 air conduction
15 seconds	C128 bone conduction

July-August, 1936. Conversation, 4 meters.

Apart from the improvement in his hearing the patient's general state of health has improved considerably. His former feeling of intense heaviness in the head has quite gone off. The singing in his ears has not entirely disappeared but is greatly reduced.

CASE 4.—D. S., age 41, ship owner, Oslo. Examined June and September, 1935.

No inherited otosclerosis. Bilateral progressive reduction of hearing for ten years. Various treatments by several physicians without effect. Bilateral exostosis. Tympanic membranes normal.

Handles of the malleus movable. X-ray: Normal pneumatization, no pneumatization of the apex.

9. 6, 1935.—Hearing test.

Right		Left
0	Whisper	
0.20 metre	Conversation	0.40 meter
C256	Lower limit of tone	C128
0	C128 air conduction	1—2 sec. (normally 120)
40 sec.	C128 bone conduction	35 sec. (normally 35)

9. 7, 1935.—Operation for otosclerosis. The operation was carried out on the right ear, which presented prolonged bone conduction as well as the greater reduction of hearing and the more rapid progression. Healing per primam. Length of stay in hospital, nine days.

GUNNAR HOLMGREN

3. 30, 1936.—Hearing test. Right ear.

Whisper	0.40 meter
Conversation	10 meters
Lower limit of tone	'64
C ₁₂₈ air conduction	10 seconds
C ₁₂₈ bone conduction	45 seconds

Before the operation the patient could hardly hear, even with a bone conduction telephone held to the left ear. Since the operation this apparatus has no longer been needed. The patient hears now well enough to carry on his large business. He takes part in meetings and social life. He feels no giddiness whatsoever in daily life. He is a keen sportsman and skis without difficulty.

CASE 5.—A. K., age 22, woman. Examined August 1935 and January-August, 1936. No inherited otosclerosis. Bilateral progressive reduction of hearing during the past year. Painful singing in her ears. Paracusis Willisii. Treated without effect. Tympanic membranes normal, normally movable. X-ray; Normal pneumatization, no pneumatization of apex.

5. 5, 1936. Hearing test.

Right		Left
0	Whisper	0
0.5 meter	Conversation	0.3 meter

5. 6, 1936.—Operation for otosclerosis on the left ear.

7. 14, 1936.—Hearing test. Left ear.

Whisper, 0.2 m.
Conversation, 10 m.

Since 7. 14, a rapid reduction of hearing in the ear operated upon.

8. 3.—Hearing test.

Right		Left
0.1 meter	Whisper	0
0.5—1 meter	Conversation	0.2—0.5 meter
C ₁₂₈	Lower limit of tone	C ₁₂₈
7 seconds	C ₁₂₈ air conduction	4 sec. (normally 120)
40 seconds	C ₁₂₈ bone conduction	40—45 sec. (normally 45)

8. 3.—Operation for otosclerosis (revision) on the left ear. Healing per primam. Length of stay in hospital, fourteen days.

8. 13.—Hearing test. Left ear.

Whisper	0.2—0.3 meter
Conversation	> 10m. meters
Lower limit of tone	C ₃₂
C ₁₂₈ air conduction	40 seconds (normally 120)
C ₁₂₈ bone conduction	70 seconds (normally 45)

CASE 6.—S. K., age 48, merchant, Oslo. Bilateral progressive reduction of hearing for sixteen years. Continual singing in the ears. Paracusis Willisii. Treated without effect. Used an ear trumpet. Tympanic membranes normal. Handles of the malleus immovable. X-ray, normal pneumatization. No pneumatization of apex.

THE SURGERY OF OTOSCLEROSIS

6. 17, 1936.—Hearing test.

Right		Left
0	Whisper	0
0.6 meter	Conversation	0.6 meter
C128	Lower limit of tone	C128
9 seconds	C128 air conduction	13 sec. (normally 120)
80 seconds	C128 bone conduction	70 sec. (normally 45)

6. 17, 1936.—Operation for otosclerosis on the right ear. Healing per primam. Length of stay in hospital, nineteen days.

6. 26, 1936.—Hearing test. Right ear.

0.40 metre	Whisper
27 meters	Conversation
C32	Lower limit of tone
65 seconds	Air conduction
80 seconds	Bone conduction

The indications are simple. With a view to results, all cases may be operated upon who have a pronounced reduction in hearing with a raised lower tone limit, negative Rinne, prolonged or at least not shortened Schwabach, a normal drum membrane and roentgenologically normal middle ear, i. e., cases of high grade otosclerosis without labyrinthine degeneration.

A pronounced reduction I regard as one which renders the patient unable to follow his vocation; generally speaking, one meter or less conversation. One can be certain of improving this limit. As my records show, prolonged bone conduction is not necessary for good prognosis nor is an entirely normal drum membrane.

The technic is equally simple, although still in the stage of development. In principle, it is a decompression of peri- as well as endolymph by the production of a fistula which is covered with a soft, resilient tissue.

At one operation, which I performed in 1920, I made the following observation. I operated under the microscope on the promontory, made a flap of mucoperiosteum, with its base forward, and pushed this flap forward with a small raspator. This brought forth a hair-line stream of clear labyrinthine fluid from a pre-formed fine lumen definitely anterior and somewhat inferior to the fenestra ovalis. This lumen was so small that it could not be seen even with the magnification of ten diameters. There was an immediate and pronounced improvement in the patient's hearing without the labyrinth having been uncovered at any point. This preformed canal may have been the fistula ante fenestram described by Otto Mayer and Gordon Wilson.

Through this operation it was determined that a decompression of the labyrinthine fluid can improve the hearing. At every operation for otosclerosis that I have done under the microscope since then I have observed that the fluid escaped as soon as the fistula was begun and before the endosteum, so far as could be determined through the microscope, was perforated. Sourdille made the same observation. This decompression of the perilymph I believe can play a role in the sudden improvement which the fistula brings about.

The same holds good for decompression of the endolymph. If one, before reaching the semicircular canals, uncovers the anterior lateral wall of the saccus endolymphaticus there is in some cases—not in all—a prompt and perceptible, if not a high grade improvement in the hearing.

The operative technic was as follows: Under a local anesthetic a wide antrotomy is performed with most careful hemostasis. Bleeding from the bone is slight, nevertheless it is carefully stopped with bone wax. The anterior lateral wall of the saccus endolymphaticus is now uncovered, when the hearing often increases to about two meters for conversation. Now, preferably with a chisel, fistulas are made to the horizontal and posterior vertical canals, sometimes also to the anterior vertical. Each fistula is made fairly long, four to five millimeters, the endosteum is removed without injuring the membranous labyrinth and the fistulas are widened as much as possible. As soon as the fistula reaches a canal, the hearing increases promptly and constantly; in fact, all patients afterward hear conversation at the greatest distances that my operating room, together with the adjoining room, permits—that is, about ten meters. Now the aditus ad antrum is enlarged and a soft prothesis is laid into the antrum which on the one hand prevents the collection of blood and wound secretions and on the other supplies an elastic wall for the fistula and which should crowd the fistula somewhat to prevent it from closing during the period of healing. As protheses I have employed various substances: a thin rubber bladder (filled with air, with physiologic salt solution or with fat), a piece of gutta percha or, more recently, fat. In order to prevent the undesired growth of fat to the membranous labyrinth I have in several cases coated the antrum wall with leaf gold before the fat prothesis was laid in. The incision was closed with Michel clips. The operation is done under aseptic precautions and healing per primam follows.

Although it will not be possible here to recount the details of the various operations, I shall touch upon a few of the more important ones.

THE SURGERY OF OTOSCLEROSIS

Since February, 1935, I have operated upon thirty-four patients with various modifications of this technic; of these, thirteen cases (ten women and three men) received fat prostheses with leaf gold over the fistulas. Among these cases there occurred no severe complication and no death. Only in the beginning was there some vertigo. In individual cases this was quite pronounced for about a week. Usually it is mild, even in the beginning. The vertigo disappeared at latest after one month.

Those patients who previous to the operation complained of tinnitus state that this disappeared entirely or almost entirely with the establishment of the fistula. In those cases in which the auditory improvement is reduced and eventually disappears during healing, tinnitus recurs. There appears to be, in these cases, a certain parallelism between reduction in hearing and tinnitus.

The improvement in hearing at the time of operation is constant and astonishing. In that moment in which the fistula is established, the hearing increases for conversation in practically all cases to at least ten meters, rarely somewhat less. When the patient, after resting a few hours following operation, is examined in one of the corridors of the hospital, he repeats conversation heard at a distance of twenty, thirty and sometimes even forty meters. During the period of healing, the hearing is reduced in some cases to the preoperative state; in two cases it was reduced even further. In the majority of cases, in spite of this, a greater or lesser improvement in hearing is attained which in certain cases is even progressive. It is only after many years' observation that one may speak of a permanent improvement in hearing; until then I will content myself with stating that in the thirteen patients treated with fat prosthesis and gold leaf, eleven have improved, eight of them to a pronounced degree. A reliable estimate of hearing requires experience as well as care and exactitude. It is well known that hearing in otosclerosis undergoes wide fluctuations. The general status of the patient, passing nervousness, variations in the weather and so on, affect it. The surroundings, the examiner and the method of conducting the test naturally play an equally important role in the result.

My cases have all been examined by two examiners, by the same methods, once in a soundproof room and once under ordinary surroundings. Aside from this, audiograms were made in the camera silentia. In no case was the hearing recorded without many confirmatory tests having been made.

The operative technic here given is simple. It recommends itself as safe and not very time-consuming and yields in practically all cases a definite improvement in hearing which, during healing, is again somewhat reduced. Over a period of one and one-half years a certain improvement in hearing has persisted in the majority of cases, in most of them quite pronounced. Years must elapse before this may be demonstrated to be permanent.

This work is the result of long experience with experimental animals. How shall the fistulæ be made in order to produce the greatest primary improvement in hearing and how shall they later be handled in order to achieve the greatest permanent good? Those are the two important questions demanding attention. Once these are answered, one may expect that the surgical management of otosclerosis will be successful in the hands of those who can maintain the necessary asepsis.

TRACHEOBRONCHIAL OBSTRUCTION FROM ESOPHAGEAL CARCINOMA: BRONCHOSCOPIC TREATMENT WITH NEODYMIUM:YTTRIUM-ALUMINUM-GARNET LASER

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Tracheobronchial obstruction resulting from esophageal carcinoma is uncommon. Patients with advanced esophageal carcinoma with tracheobronchial obstruction usually present with severe dyspnea or hemoptysis or both and may die of suffocation. The Lahey Clinic experience using laser bronchoscopy for the palliation of symptoms of airway obstruction in patients with esophageal carcinoma is presented. From 1982 to 1990, nine patients were treated in 13 procedures using the neodymium:yttrium-aluminum-garnet laser. Of the patients, seven had undergone previous treatment of the primary tumor. Tumors were located in the trachea in seven patients and in the main stem bronchi in three patients. Improvement of the airway caliber was achieved in all patients with relief of the dyspnea. The mean hospital stay was 2 days. One patient lived 4 years after laser treatment with no recurrence of tumor, and one patient died 1 week after treatment as a result of his poor general condition. The rest of the patients lived 3 to 41 weeks, with a median survival of 35 weeks. No complications were related to the procedures, and in particular, no tracheoesophageal fistulas developed. Our experience indicates that bronchoscopic application of this laser in conjunction with other treatment modalities can improve the quality and duration of life in selected patients with esophageal carcinoma that invades and obstructs the trachea.

KEY WORDS — bronchoscopy, endobronchial neoplasms, endoscopic laser therapy, esophageal carcinoma, lasers, stenosis, trachea.

INTRODUCTION

Since the introduction of laser technology for the endoscopic treatment of patients with tracheobronchial disorders in 1973,¹ this technique has gained acceptance for palliation of symptoms in patients with tracheal obstruction secondary to primary or metastatic tumor. Lasers of various wavelengths have proved to be precise, powerful, and relatively safe tools for the endoscopic management of lesions obstructing the airway.^{2,3} The effectiveness and safety of laser application for palliation of obstruction of the airways by malignant tumor were enhanced after the introduction of the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser.³⁻⁶ The excellent hemostatic qualities of this laser's wavelength make it the most suitable laser for endoscopic removal of malignant tracheobronchial lesions. At the Lahey Clinic Medical Center,⁷ we have used laser bronchoscopy for more than 7 years in more than 400 procedures for the treatment of 269 patients with obstructing lesions of the airway, and we have had a high success rate in relief of symptoms with a complication rate of 7%.

In our experience, carcinoma of the esophagus is the second most frequent metastatic lesion involving

the trachea and bronchi, after renal cell carcinoma, and it produces obstruction of the central airways by direct extension from the primary tumor or from local mediastinal nodes rather than by hematogenous spread as seen in other metastatic carcinomas. We present our experience with the treatment of nine patients with esophageal carcinoma obstructing the upper and lower airways.

PATIENTS, MATERIALS, AND METHODS

Nine patients with carcinoma of the esophagus were referred for bronchoscopic laser therapy because of severe or rapidly deteriorating dyspnea, persistent hemoptysis, uncontrolled cough, or post-obstructive pneumonia from tracheal or bronchial obstruction by tumor. All patients underwent diagnostic fiberoptic bronchoscopy, which was performed either by the referring physician or by a member of our laser team. All patients had a complete history taken and underwent physical examination. Because most of the patients in this series had recurrent tumor and had been treated in the past, their disease was usually well documented. All patients underwent preoperative computed tomography (CT) of the chest,

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Presented at the meeting of the American Broncho-Esophagological Association, Waikoloa, Hawaii, May 5-6, 1991.

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PATIENT CHARACTERISTICS AND FOLLOW-UP DATA

Patient No.	Age	Sex	Previous Therapy	Radiographic Findings	Site	No. of Procedures	Survival From First Laser Treatment (wk)
1	72	F	Surgery	Normal	Trachea, LMS	1	1
2*	67	M	None	Normal	RMS, LMS	1	224
3	62	M	XRT	Stenosis	Trachea	1	24
4	52	F	Surgery, XRT	PI	Trachea	3	41
5	71	M	XRT	Stenosis	Trachea	2	21
6	68	M	Surgery, XRT	Stenosis	Trachea	1	18
7	67	M	XRT	Stenosis	Trachea	1	3
8	62	M	XRT	Stenosis	Trachea	2	60
9	54	F	Surgery, XRT	Stenosis	RMS	1	54

All patients showed improvement, and no patients had complications.

XRT — radiotherapy, PI — parenchymal infiltration, LMS — left main stem bronchus, RMS — right main stem bronchus.

*Still alive.

CT of the trachea, and determination of arterial blood gases and pulmonary function tests.⁸

Of the patients, six were men and three were women, ranging in age between 52 and 72 years (median, 67 years). The most common site of obstruction was the trachea (seven patients). Results of radiographic examination (CT) were normal in two patients, showed tracheal narrowing in six patients, and showed infiltration of paratracheal soft tissue in one patient. Before application of Nd:YAG laser therapy, three patients had surgery and radiotherapy, four patients had radiotherapy alone, and one patient had surgery alone. One patient, who was not treated previously, presented with severe obstruction that required immediate treatment with the Nd:YAG laser followed by radiotherapy (see Table). All patients were treated in an operating room under general intravenous anesthesia (thiopental sodium) and manual Venturi jet ventilation.

A ventilating rigid bronchoscope (Karl Storz Endoscopy-America, Culver City, Calif) was used with a Hopkins 0° telescope. A 100-W Nd:YAG laser system was used (Cilas, Compagnie Industrielle des Lasers, Marcoussi, France, or LaserSonics model 8900, Heraeus LaserSonics, Inc, Milpitas, Calif). The laser energy was delivered through a coaxial quartz fiber 2.4 mm in diameter. The laser power delivered ranged between 20 and 40 W, and the laser pulse duration varied between 0.7 and 1.0 second. The laser fiber tip was held 0.5 to 1.0 cm from the tumor. After initial photocoagulation, the tumor was resected with the tip of the rigid bronchoscope and removed with a suction catheter or biopsy forceps. The base of the tumor was photocoagulated with the laser to ensure hemostasis.

Patients with extrinsic compression by tumor mass

were not treated with this method because of the high risk of perforation. Care was taken not to vaporize the mucosa of the posterior tracheal wall, thus leaving some tumor mass adjacent to the tracheal wall to avoid the development of a tracheoesophageal fistula (see Figure). A lumen size 70% of normal was considered adequate to provide sufficient palliation of dyspnea and to permit drainage of secretions. The surgical technique, methods of anesthesia, and safety precautions for Nd:YAG laser bronchoscopy have been described previously.^{8,9}

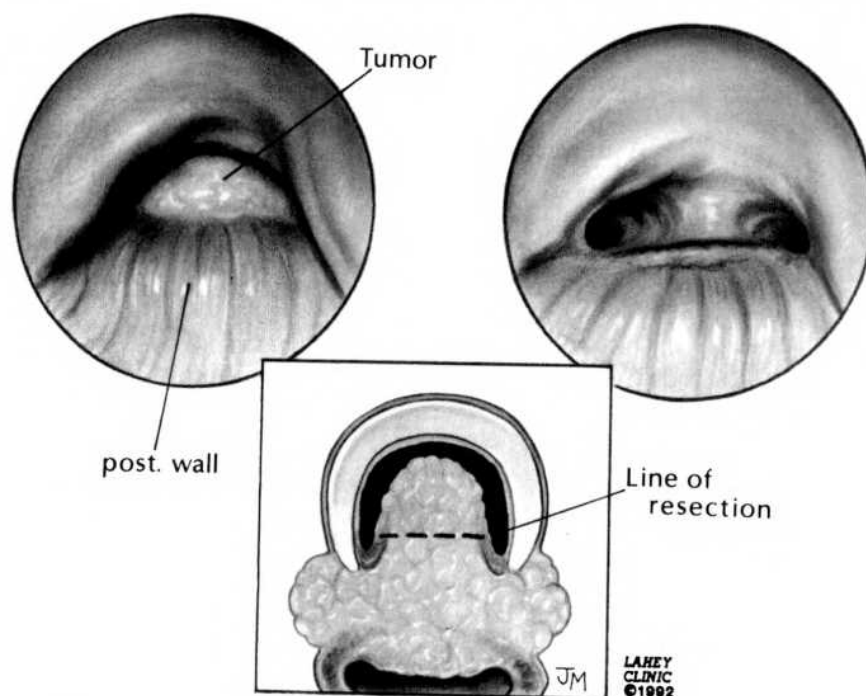
RESULTS

Dyspnea was the primary symptom and the main indication for operation in all patients. Nine patients with tracheobronchial obstruction were treated in 13 procedures, the number of procedures for each patient ranging from 1 to 3. The mean operative time was 53 minutes (25 to 85 minutes).

Symptoms improved immediately after operation in all patients. One patient who required assisted ventilation before operation was successfully extubated. In three patients, symptoms recurred 7, 16, 33, and 50 weeks after operation and improved after repeated treatments. In nearly all instances, physical examination and performance status confirmed the subjective impression. No dysphagia occurred before or after treatment, and patients were able to start oral intake immediately after operation.

One patient lived 224 weeks without symptoms with no evidence of disease, and one patient lived 1 week. The median survival time was 49.5 weeks from the time of first treatment. Obstruction of the airway was not present in any patient at the time of death.

No complications related to the technique or to the



Tracheal invasion by esophageal carcinoma before and after laser therapy. Viable tumor remains along posterior tracheal wall. Laser resection in this area has been limited to prevent perforation. (Reproduced with permission of Lahey Clinic.)

use of the laser occurred. No pneumothorax, no pneumomediastinum, and no tracheoesophageal fistulas developed.

The Figure shows typical tracheal invasion by esophageal carcinoma before and after laser therapy.

DISCUSSION

Most patients who present with lesions that obstruct the central airways have a tumor that is inoperable because of mediastinal involvement or is in a location that is too central for surgical resection. These patients often have profound dyspnea, uncontrolled hemoptysis, or postobstructive sepsis.

Various treatment modalities have been advocated for the treatment of patients with esophageal carcinoma, such as chemotherapy, ionizing radiation therapy, surgical resection, salivary bypass, dilation, or insertion of a prosthetic device. However, none of these treatments achieve a high percentage of good results. Use of these therapeutic modalities usually provides palliation of symptoms for a short period; however, the tumor frequently recurs after a few months. According to the literature,^{10,11} survival rate can vary from 1 to 20 months.

In selected patients, Nd:YAG laser treatment of an obstructing tracheobronchial malignant process can provide a relatively long period of survival without symptoms. In a series of 116 patients with 176 laser applications, Brutinel et al¹² indicated that the quality and duration of life were improved in patients with obstructing carcinoma who were treated with laser

bronchoscopy.

The mechanism of airway obstruction that results from esophageal carcinoma can be the result of direct extension of the tumor anteriorly, invading and obstructing the tracheal lumen, or of external compression of the posterior membranous tracheal wall, or a combination of these two mechanisms. Invasion of the recurrent laryngeal nerve by the tumor can also cause unilateral or bilateral vocal cord paralysis and airway obstruction. Further compromise of the airways can be caused by aspiration owing to cervical esophageal obstruction or a tracheoesophageal fistula, leading to poor pulmonary function.

In a review⁷ of malignant lesions obstructing the trachea, the most common metastatic lesions to the trachea were renal cell (12), esophagus (7), colon (7), breast (3), stomach (1), endometrium (1), ovary (1), thyroid (1), melanoma (1), ameloblastoma (1), and larynx (1). Esophageal carcinoma produced obstruction of the central airways by direct extension from the primary tumor or from local mediastinal nodes rather than by hematogenous spread as seen in other metastatic carcinomas.

Our philosophy regarding indications and techniques of laser therapy is similar to that outlined by Dumon.¹³ Patients with lesions of the trachea, carina, or main stem bronchi usually require treatment because these lesions produce severe symptoms that warrant therapy despite the inherent risks associated with the procedure. An absolute contraindication to Nd:YAG laser treatment is the presence of extrinsic compression of the airway either by the tumor mass

or by mediastinal lymph nodes. The presence of a tracheoesophageal fistula and coexistent vocal cord paralysis, especially bilateral, are relative contraindications.

The most common complications associated with laser ablation of an endotracheal tumor are hemorrhage from a highly vascular tumor or perforation of a large vessel and perforation of the trachea resulting in pneumothorax, pneumomediastinum, emphysema, and mediastinitis. The risk of perforation is high when extrinsic compression is present, and laser treatment is contraindicated in this instance.

A challenge in the treatment of patients with esophageal tumor with local extension to the trachea is to avoid the creation of a tracheoesophageal fistula. The risk of perforation of the posterior wall of the trachea is high, especially in the presence of extrinsic compression. All of our treated patients had local invasion of the tracheal wall by tumor. Special care was taken

to leave tumor attached to the tracheal wall to prevent the development of a fistula resulting from laser-induced tumor necrosis.

Survival data are difficult to interpret in our group of patients with advanced carcinoma because a prospective controlled study is impossible. Because palliation of symptoms is the main goal of this procedure, quality of life and successful relief of symptoms are more important to analyze than survival data.

CONCLUSION

Our small series shows that laser photocoagulation of tracheal obstruction resulting from metastatic or locally invading esophageal carcinoma can be treated effectively by Nd:YAG laser photocoagulation. This technique offers quick and sometimes relatively long-lasting relief for selected patients with esophageal carcinoma. The treatment can be repeated without increase in operative risks or complications.

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TRACHEAL AGENESIS

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Tracheal agenesis is a catastrophic congenital anomaly that invariably results in death. Forty-seven cases have been previously reported in the literature. We add five additional cases, including two type 1 cases, two type 2 cases, and one type 3 case, based on Floyd's classification scheme. We describe the features of this unusual anomaly at the time of diagnosis. We discuss a rational approach to the management of this difficult problem on an emergent basis that allows for the maintenance of the infant's life until all of the implications of this fatal condition can be assessed. While we do not advocate reconstructive surgery for this anomaly, which has been universally fatal, we discuss the potential rearrangement of the anatomy, which may offer some hope in future cases. The concomitant congenital anomalies associated with these cases are reviewed, and autopsy specimens are presented for their anatomic interest.

KEY WORDS — congenital anomaly, tracheal agenesis.

INTRODUCTION

Tracheal agenesis is a rare congenital anomaly that is universally fatal. Since it was first described by Payne¹ in 1900, there have been 47 cases reported in the literature.² Floyd et al³ classified tracheal agenesis into three variants depending on the relationship between the trachea and the esophagus (Fig 1³). In type 1, a short segment of distal (toward the center of the body) trachea arises from the anterior wall of the esophagus before dividing into the main stem bronchi. In type 2, there is complete tracheal agenesis, with a communication between the esophagus and the carina from which the two main stem bronchi take their origin. In type 3, the two main stem bronchi arise individually from openings in the anterior esophageal wall. The incidence of type 1 tracheal agenesis is 13%, the incidence of type 2 is 65%, and the incidence of type 3 is 22%.² This report presents five additional cases treated by the authors between 1986 and 1989.

CASE REPORTS

Case 1. A male child was born by cesarean section

at 31 weeks of gestational age (1,480 g) at the Albany Medical Center Hospital. One month before delivery, the mother was treated for premature labor and ultrasound examination showed polyhydramnios and duodenal atresia. Following delivery there was immediate respiratory distress. Efforts at intubation were unsuccessful because of an inability to visualize the vocal cords at direct laryngoscopy. An emergent tracheotomy was attempted; however, no tracheal arches could be identified. A tentative diagnosis of tracheal agenesis was made and a tracheotomy tube was placed in the esophagus. With the child transiently stabilized, a more detailed examination of the airway was made with topical anesthesia in the neonatal intensive care unit. Laryngoscopy revealed a rudimentary epiglottis, which blended into the lateral pharyngeal walls. There was absence of the arytenoids, vocal cords, and cricoid. There was no trachea below the epiglottis, the pharynx being continuous with the esophagus. In the distal (toward the center of the body) esophagus, approximately 5 cm below the introitus, an opening was seen into a small cavity that

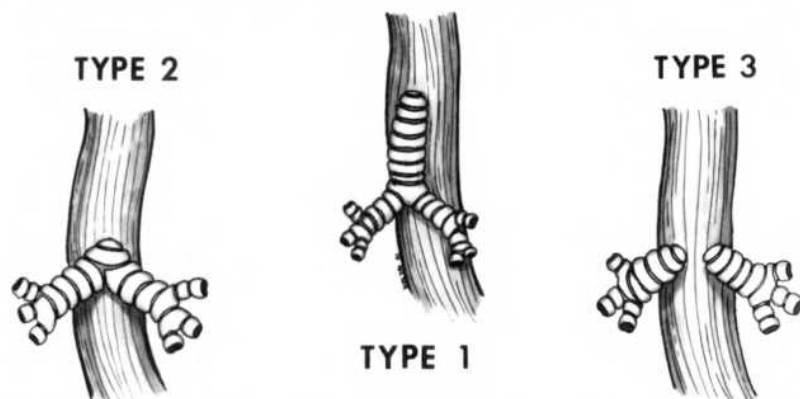


Fig 1. Illustration of classification scheme of Floyd et al.³

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Presented at the meeting of the American Broncho-Esophagological Society, Waikoloa, Hawaii, May 5-6, 1991.

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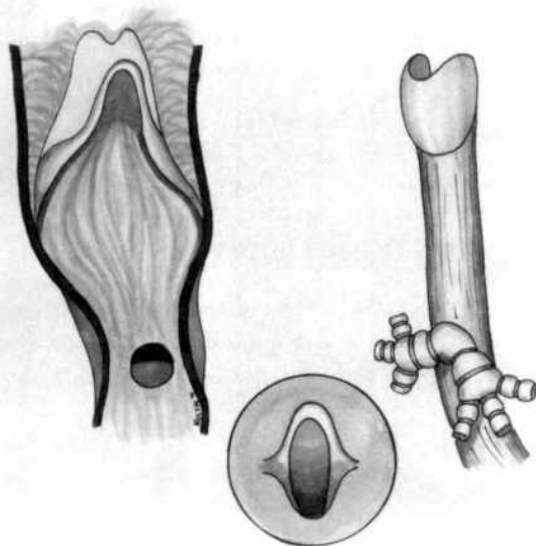


Fig 2. Type 2 tracheal agenesis as seen in case 1. On right is anterior view, showing abnormal thyroid cartilage and absence of cricoid cartilage. Carina and main stem bronchi take origin from middle portion of esophagus. On left is posterior view, demonstrating absence of laryngeal structures and trachea, as well as carinoesophageal fistula in middle portion of esophagus. In middle is view of pharynx seen at endoscopy.

gave rise to the main stem bronchi (Fig 2). A nasogastric tube was placed to decompress the stomach of air and reduce gastric acid soiling in the airway. Reconstruction was felt to be inappropriate, the child's condition deteriorated, and he died 2 days after birth.

Postmortem examination confirmed the endoscopic findings. There was laryngeal atresia, tracheal atresia, and duodenal atresia. Other anomalies included agenesis of the right kidney, right urethra, and right renal artery. In the heart there was a ventricular septal defect, a patent foramen ovale, and atresia of the pulmonary valve. There were hemivertebra of the T-10 vertebral body and low-set ears.

Case 2. A female child was delivered by cesarean section at 35 weeks' gestational age (2,280 g) at the Albany Medical Center Hospital. The pregnancy was complicated by borderline diabetes mellitus and by hypertension. Prenatal ultrasound showed polyhydramnios, hydrocephalus, and breech presentation. After delivery the infant experienced immediate respiratory distress and was intubated; however, the endotracheal tube was repeatedly dislodged into the esophagus. Direct laryngoscopy and bronchoscopy were performed in the neonatal intensive care unit with topical anesthesia. The vocal cords were normal; however, there was a 2-cm laryngotracheoesophageal cleft. An endotracheal tube passed between the cords was dislodged into the esophagus at

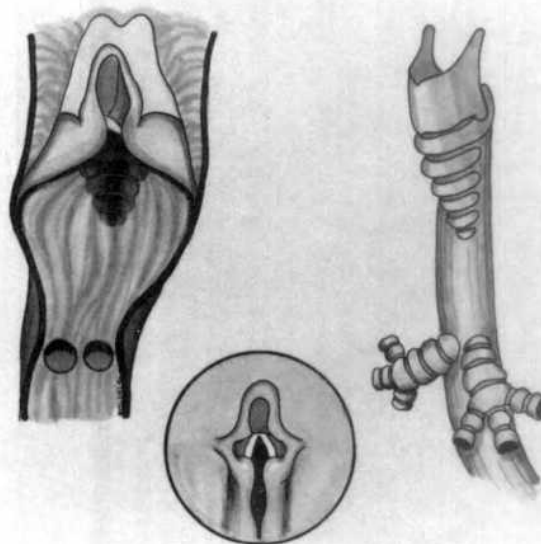


Fig 3. Type 3 tracheal agenesis as seen in case 2. On right is anterior view, with normal-appearing larynx and shield of cartilaginous arches below cricoid cartilage. Originating from central portion of esophagus are two main stem bronchi. On left is posterior view, demonstrating laryngotracheoesophageal cleft, absence of upper trachea, and two bronchoesophageal fistulas in middle portion of esophagus. In middle is endoscopic view, demonstrating normal appearance of supraglottis, with presence of laryngotracheoesophageal cleft.

the base of the cleft. Bronchoscopy showed a trachea ending 2 cm below the glottis with a fistula to the esophagus. Four centimeters below the base of the cleft, two small openings were seen in the anterior esophageal wall, from which arose the two main stem bronchi (Fig 3). A nasotracheal tube was measured to extend down to these openings and placed into the esophagus, and the child was mechanically ventilated. Nevertheless, the child's condition deteriorated and she died several hours after birth.

Postmortem examination confirmed the endoscopic findings. Other anomalies included an Arnold-Chiari malformation with hydrocephalus and meningocele, an atrial septal defect, a rudimentary stomach, posterior fusion of the right and left lungs, microsplenia, and multiple enteric cysts in the esophagus and small bowel.

Case 3. A female child was born at 40 weeks' gestational age (3,012 g) at Newham Hospital in London. The infant developed immediate respiratory distress. An attempt was made to intubate the child, but this was unsuccessful and she was emergently transferred to the Hospital for Sick Children at Great Ormond Street and brought to the operating room, where another attempt at intubation failed. Direct laryngoscopy revealed a total glottic web, which prompted an emergent tracheotomy under general

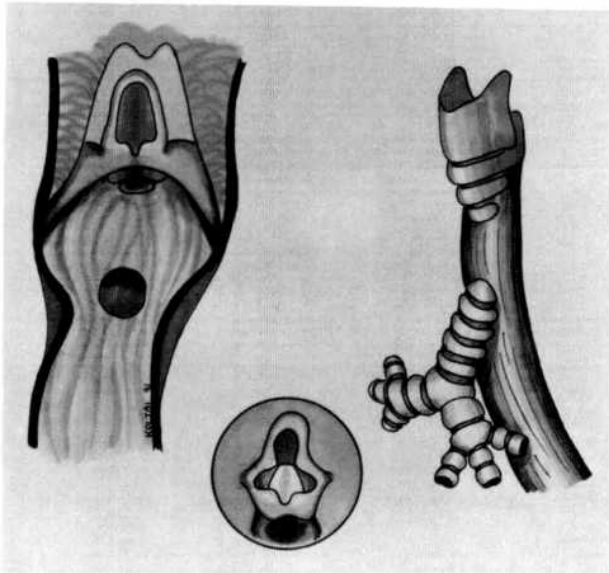


Fig 4. Type 1 tracheal agenesis as seen in case 3. On right, distal tracheal stump is seen arising from upper end of thoracic portion of esophagus. On left, posterior view demonstrates absence of upper trachea, with rudimentary tracheal rings. There is lack of communication between supraglottis and subglottis. Communication between thoracic esophagus and distal tracheal stump is seen. In middle is endoscopic view demonstrating total glottic web in what appeared to be otherwise normal larynx.

anesthesia administered by face mask. No trachea could be found on neck exploration; however, dissection in the region of the larynx, just below the cricoid, revealed a small shieldlike section of cartilage, approximately 1 cm in length and terminating in the anterior esophageal wall. This was believed to represent tracheal agenesis. An incision was made into the upper esophagus at the level of the tracheotomy site, and a Hopkins rod telescope was passed into the esophagus. Approximately 3 cm below the esophagostomy, an opening in the anterior esophageal wall was seen. This connected to a short section of trachea that was several centimeters long and that bifurcated into the two main stem bronchi (Fig 4). Once the anatomy of the child's anomaly was clear, a 3.0 endotracheal tube was slipped onto a Hopkins rod telescope and passed through the esophagostomy into the distal tracheal stump under direct vision. The Hopkins rod was removed and the endotracheal tube left in position. The edges of the esophagostomy were then sutured to the skin to create a pseudotracheotomy, and a custom tracheotomy tube was fashioned. A nasogastric tube was then passed and placed on suction drainage to keep gastric secretions from soiling the respiratory tract. After discussion with the father it was felt that no further surgical intervention should be undertaken. The child was then transferred back to her mother's side, at Newham Hospital, where she died 2 days later. No autopsy was obtained.

Prior to discharge from the Hospital for Sick Children, a thorough physical examination was made, and no other congenital anomalies were found.

Case 4. A male child, one of twins, was born at 34 weeks' gestational age (1,350 g) at the Albany Medical Center Hospital. He showed signs of immediate respiratory distress and was intubated; however, the endotracheal tube was repeatedly dislodged into the esophagus. A direct laryngoscopy and bronchoscopy were performed with topical anesthesia in the neonatal intensive care unit. Examination revealed normal vocal cords, a 3-cm laryngotracheoesophageal cleft, a 2-cm segment of subglottic trachea with a fistula into the esophagus at the base of the cleft, a 1-cm section in which the trachea was absent, and a lower tracheal segment that exited from the anterior esophageal wall and connected to the main stem bronchi. Once the diagnosis of laryngotracheoesophageal cleft and tracheal agenesis was made, a 3.0 endotracheal tube was threaded onto a 2.7-mm Hopkins rod telescope, and under direct visual control, the distal tracheal segment was approached through the esophagus and intubated. The Hopkins rod was withdrawn and the child was successfully ventilated. A nasogastric tube was placed and kept on suction drainage to decompress the stomach and prevent gastric acid soiling of the airway. Despite intubation, refractory hypoxemia persisted with a large alveolar-arterial gradient suggestive of a shunt. On secondary survey, a systolic murmur was heard. An echocardiogram demonstrated a tetralogy of Fallot with 70% overriding aorta and severe pulmonic stenosis. The significant anomalies of both the cardiovascular and respiratory systems suggested a very poor prognosis, and surgical intervention was deemed inappropriate. The child died on the fourth hospital day.

On postmortem examination the endoscopic findings were confirmed. Other findings included a small azygous lobe in the right lung, a right side aortic arch, and duodenal atresia. The dissection of the heart revealed pulmonary atresia, a large patent ductus arteriosus, and atrial and ventricular septal defects.

Case 5. A male child was born at 30 weeks' gestational age (1,520 g) at the Royal Sussex Hospital, Brighton, England. The infant developed immediate respiratory distress. An attempt was made to intubate the child; however, an endotracheal tube could not be passed through what appeared to be a glottic web. An emergent tracheotomy was attempted, but no tracheal arches could be identified. The hollow viscus of the esophagus was entered and an endotracheal tube was passed into the esophagostomy, through which the child's ventilation was maintained for a short period of time. However, the child's condition

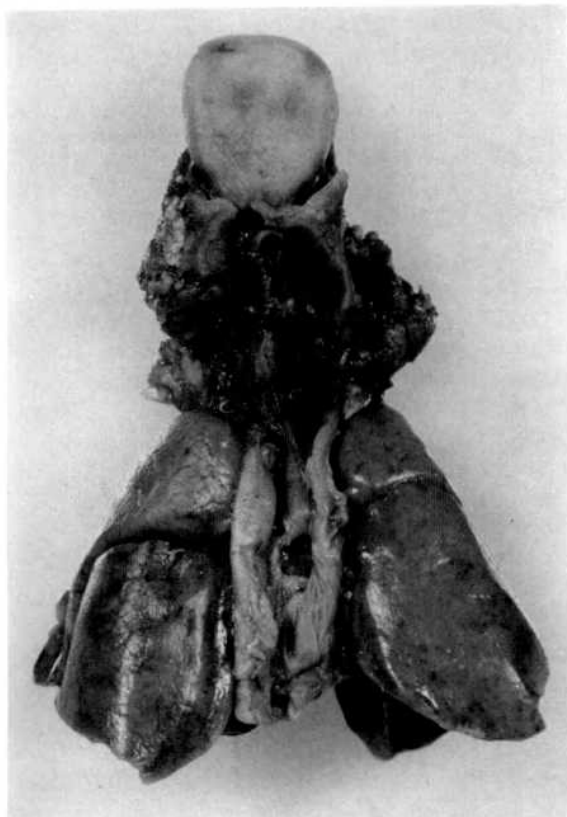


Fig 5. (Case 5) Type 2 tracheal agenesis. Posterior view of total autopsy specimen with esophagus open posteriorly. Rudimentary larynx is seen at base of tongue. Carino-esophageal fistula is seen in lower portion of esophagus.

rapidly deteriorated and he died several hours after birth.

On postmortem examination an infantile larynx was noted (Fig 5) that was filled with a solid core of tissue. Below the level of the cricoid cartilage there were no tracheal rings, and this core of tissue, which was filled with glandular material, dissipated approximately 2 cm below the level of the cricoid (Fig 6). The esophagus appeared normal; however, there was a large fistula between the esophagus and the carina, from which the two main stem bronchi took their origin. The other anomalies noted were duodenal atresia and a low-set, rudimentary right pinna.

DISCUSSION

Rare are the moments in the practice of medicine that compare with the anxiety produced when confronting a newborn infant in respiratory distress. This time of joy, so promising of life, rapidly deteriorates to tragedy unless appropriate steps are taken to secure the child's airway, generally by passing an endotracheal tube. Often, the cause of the child's distress will become apparent during an attempt at intubation.

There are many causes of neonatal respiratory



Fig 6. (Case 5) Photomicrograph at level of cricoid cartilage. Lumen is full of stroma and glandular elements.

distress; however, very few present with the immediacy, persistence, and severity of tracheal agenesis. While there may be periods of clinical stability, the overall trend is a progressive deterioration of respiratory function. One of the helpful signs suggestive of this rare anomaly is a weak (cases 2 and 4) or absent (cases 1, 3, and 5) cry in conjunction with vigorous but futile respiratory effort. Another useful clue is the ability to ventilate the infant with positive pressure from an Ambu bag. However, the most consistent finding for tracheal agenesis among our patients was the inability to pass or maintain an endotracheal tube.

Once the diagnosis is suspected, it can be confirmed in several ways. The simplest way is to pass an endotracheal tube 5 cm into the esophagus and provide positive pressure manual ventilation. This will usually relieve the distress and transiently stabilize the infant's condition while a plan of action is formulated. Diagnostic laryngoscopy and bronchoscopy should be performed in order to delineate the anatomy. An attempt at emergent tracheotomy is often the first surgical action taken (cases 1, 3, and 5), generally when the child cannot be intubated because of concomitant laryngeal agenesis. This typically becomes a puzzling neck exploration, since the trachea cannot be found. Whether neck exploration should be elec-

tively undertaken to elucidate the anatomy and confirm the diagnosis is debatable. Diaz et al² suggest that since tracheal agenesis has a fatal prognosis, neck exploration should be done to rule out less severe and possibly correctable anomalies. However, our experience suggests that careful endoscopy will provide similar information.

The occurrence of laryngeal anomalies in association with tracheal agenesis has been previously reported.⁴ We observed laryngeal malformations in all our infants, including laryngotracheoesophageal cleft in cases 2 and 4, complete laryngeal agenesis with only a rudimentary epiglottis in case 1, total webbing of the vocal cords in case 3, and laryngeal agenesis with an elliptically formed cricoid ring and a glottic opening filled with a solid core of tissue composed of glandular elements in case 5.

The association of tracheal agenesis with other multiorgan congenital malformations has been a topic of interest.⁵⁻⁸ VATER association was initially described by Quan and Smith⁹ as a nonrandom association of anomalies consisting of vertebral defects, anal atresia, tracheoesophageal fistula and/or esophageal atresia, radial dysplasia, and renal defects. Expanded to include cardiac and limb defects, this syndrome is known as the VACTERL association.^{10,11} Effmann et al⁷ suggested a nonrandom association between tracheal agenesis and other multisystem abnormalities that occur in a similar time frame during embryogenesis. Anderson et al⁸ reported a case of tracheal agenesis in conjunction with absence of radii and speculated whether tracheal agenesis was not a feature of the VATER association. Milstein et al⁵ described four patients with tracheal agenesis, all of whom had numerous features of the VATER association, and they proposed that tracheal agenesis be included in this grouping.

It is generally accepted that at least three of the component deformities in an association should be present to be compatible with the diagnosis. However, in their population studies, Khoury et al¹¹ found the occurrence of two defect combinations in VACTERL association to be 11 times more frequent than by chance alone, and the occurrence of three or more defects was 95 times more frequent than by chance alone. If we accept their more inclusive criteria, cases 1 and 4 would fit into this association, while cases 2, 3, and 5 would not. On the other hand, if the traditional criteria are applied, then only case 1 would fit the association.

However, questions have been raised regarding the inclusion of tracheal agenesis with both the VATER and the VACTERL associations. Evans et

al⁶ applied a technique of genetic numerical taxonomy called nodal analysis, comparing malformations associated with tracheoesophageal fistula and tracheal agenesis. Their results suggest that tracheal agenesis and tracheoesophageal fistula represent manifestations of different aspects of tracheal dysmorphogenesis. They propose that tracheal agenesis occurs as a part of a different and rare pattern of malformations that includes laryngeal atresia, ventricular septal defect, aberrant lung lobation, complex congenital heart defects, duodenal atresia, and gastric, splenic, and pancreatic abnormalities and that is referred to by Diaz et al² as TACRD association. On the basis of this analysis our cases 1, 2, 4, and 5 would meet three or more of the criteria for this association.

Such developmental studies raise interesting questions about the embryogenesis of this rare phenomenon. The theory most frequently quoted to explain the occurrence of tracheal atresia was proposed by Bremer¹² in 1957. The theory is based on Wilhelm His^{13,14} description of the developing gastrointestinal tract (1885) and respiratory tract (1887). His proposed that the foregut between the lung primordium and the lowest pharyngeal pouches is divided by a tracheoesophageal notch into the ventral trachea and the dorsal esophagus. His postulated that the tracheoesophageal notch is formed by the midline fusion of lateral ridges, a process that begins caudally and extends cephalically. Smith¹⁵ subsequently proposed the concept of the tracheoesophageal septum, which is the basis of most textbook descriptions of tracheoesophageal embryogenesis.¹⁶ Bremer¹² speculated that ventral displacement of the tracheoesophageal septum could result in agenesis of the trachea.

However, the reality of an ascending tracheoesophageal septum has been repeatedly called into question. Zaw-Tun, in a study of human embryos in the Carnegie Laboratories of Embryology, found that the "so called esophageal septum is in fact the curved primitive floor that results from the ventrocaudal outgrowth of the respiratory primordium from the caudal end of the laryngeal sulcus of the foregut."^{17(p1)} He found that the subglottis and trachea develop from a ventral outgrowth off the foregut, and saw no evidence that the trachea separates from the esophagus by an ascending endodermal septum.

Kluth et al¹⁸ studied the foregut region of chick embryos with scanning electron and light microscopy. They found no signs of lateral folds or fusing foregut wall components suggestive of a tracheoesophageal septum. Rather, their studies showed that the development of the esophagus and trachea results from a simple reduction in the size of the primitive foregut, caused by a system of folds that approximate

but do not fuse. On the basis of their morphological observations, they proposed an alternative mechanism for the three major malformations seen in the aerodigestive tract: tracheoesophageal fistula with esophageal atresia, laryngotracheoesophageal cleft, and tracheal agenesis.

In tracheoesophageal fistula and esophageal atresia, the malformation will develop when the tracheoesophageal space is dislocated ventrally while differentiating into the trachea. This results in a communication between the trachea and the distal esophagus, and atresia of the proximal esophagus.

Laryngotracheoesophageal cleft will result from a failure of the ascent of the tracheoesophageal fold, with persistence of a large tracheoesophageal space.

Tracheal atresia will result from a deformation of the foregut on the ventral side and a concomitant dorsal dislocation of the tracheoesophageal space, which differentiates into the esophagus and from which the trachea and bronchi take their origin. Some comfort is to be taken that tracheal agenesis, the most catastrophic of these malformations, is also the rarest. Why there is such a large difference in the incidence of these three anomalies is not explained by any embryologic theory.

Tracheal agenesis presents a hierarchy of problems that need to be managed. The first of these issues is diagnosis, and this has been discussed above. The second issue revolves around the early stabilization of the infant's airway while an adequate assessment can be made of other congenital anomalies. The third issue is deciding whether to attempt some type of reconstructive measure to salvage the infant.

In all cases of tracheal agenesis it is important to remember that the esophagus is a path of communication between the oral cavity and the lungs. An oropharyngeal airway in conjunction with positive pressure ventilation will provide a grace period in which one can develop a strategy for the interim management of the airway. In type 1 anomalies (cases 3 and 4), threading an endotracheal tube onto a 2.7-mm Hopkins rod telescope allows intubation of the distal tracheal stump under direct visualization. This option will not work in type 2 and type 3 anomalies, and in these circumstances intubating the esophagus with a relatively large endotracheal tube to the level just above the bronchial communication will maintain the child's airway for a while. Under all circumstances, a nasogastric tube should be placed in order to aspirate the gastric contents and reduce the likelihood of airway soiling with gastric acid. The nasogastric tube is also useful for decompressing air from the stomach, which invariably collects with

ventilation through the esophagus.

The two organ systems that require the most urgent evaluation once the airway has been stabilized are the central nervous system and the cardiovascular system. Major malformations, such as the tetralogy of Fallot (case 4) or hydrocephalus and meningocele (case 2), should preclude further consideration of therapeutic intervention. However, if no other congenital anomalies are identified, some thought should be given to a surgical rearrangement of the anatomy in order to give the infant a chance to survive.

Diaz et al,² in their excellent review of the literature on tracheal agenesis, point out that this malformation is universally fatal and advise against reconstructive surgery. Instead, they advocate making the infant as comfortable as possible until he or she dies. It is difficult to disagree with this perspective, given the dismal statistics of this deformity. Nevertheless, it is worth reviewing the two published cases in which attempts have been made at reconstruction.

In 1963 Fonkalsrud et al¹⁹ reported a case of an infant girl of normal gestational age with a type 2 tracheal agenesis in whom they attempted a reconstruction. They divided the cervical esophagus, the proximal end of which was made into an esophagostome for drainage of pharyngeal secretions, and the distal end of which they sewed to the skin to form a pseudotracheotomy; a tracheotomy tube was placed in the common tracheoesophagus. They then divided the distal esophagus below the takeoff of the main stem bronchial segments in order to isolate the trachealized esophagus from gastric secretions. For nutrition, a gastrostomy tube was placed. With this reconstruction the infant survived for 6 weeks, eventually succumbing to pneumonia. A careful analysis of this report revealed that the infant was decannulated 4 days after the operation without experiencing respiratory obstruction.

In 1972 Altman et al²⁰ reported another case in which an attempt was made to save the life of a child with tracheal agenesis. Their initial procedure was gastric division in order to isolate the gastrointestinal tract from the esophagus while the infant was maintained with an oroesophageal airway. When the child's condition deteriorated, they attempted a neck exploration and placed a pseudotracheotomy into an esophagostomy. However, the child died several hours later.

Neither of these reports gives cause for any optimism. Nevertheless, the brief success enjoyed in the case of Fonkalsrud et al¹⁹ suggests that under ideal circumstances their reconstructive design should be considered and presented as an option to the family.

In summary, we have reported five new cases of

tracheal agenesis. Two of these were type 1, two were type 2, and one was type 3. All of the infants died within days of birth. Four of the five infants had other congenital tracheal anomalies in a grouping that has been referred to as the TACRD association. Current theories for explaining the embryology of tracheal agenesis are based on dated embryologic observations, and we present an alternate theory based on contemporary embryologic data. Severe respiratory distress with dyspnea, cyanosis, and aphonia in a

newborn suggests the possibility of tracheal agenesis. The diagnosis is supported by an inability to pass or maintain an endotracheal tube in position and is confirmed with endoscopy. The need for neck exploration remains debatable. These children can be initially managed with positive pressure ventilation via an oroesophageal tube with concomitant gastric decompression with a nasogastric tube. If there are no other major congenital anomalies, consideration of reconstruction should be discussed with the family.

ACKNOWLEDGMENT — We thank Loretta Lynne Crowe for assistance in the preparation of this manuscript.

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VIDEOSTROBOSCOPY OF HUMAN VOCAL FOLD PARALYSIS

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Previous stroboscopic studies of human vocal cord paralysis have been infrequent and have lacked documentation of the site of lesion. In order to study human laryngeal paralysis, the recurrent and superior laryngeal nerves were infiltrated unilaterally with lidocaine hydrochloride in three human volunteers. Vagal paralysis was simulated by combined (superior and recurrent) infiltration in one volunteer. Additionally, 20 patients with untreated laryngeal paralysis were studied from the voice laboratory at UCLA. In addition to videostroboscopic analysis, photoglottography and electroglottography were performed and synchronized with the stroboscopic images. The most significant finding in stroboscopy of the paralyzed larynx was the asymmetry of traveling wave motion. The traveling wave on the normal vocal fold had a faster wave velocity that created a phase difference in the vibration of the two folds. The wave also traversed a greater distance along the vocal fold mucosa on the normal side. No patient or volunteer with untreated laryngeal paralysis had a symmetric traveling wave, either in superior or recurrent laryngeal nerve paralysis. Synchronization with glottography indicated that the differentiated electroglottographic waveform provides useful information about the timing of glottic opening and closure in states of asymmetric laryngeal vibration. Implications for future studies and for the diagnosis of laryngeal paralysis are discussed.

KEY WORDS — laryngeal paralysis, larynx, mucosal wave, stroboscopy, voice disorders.

INTRODUCTION

Stroboscopy has provided valuable insights into laryngeal vibration and mucosal motion. However, few studies have systematically assessed the findings of stroboscopic analysis in laryngeal paralysis. Stroboscopy has a long history of clinical use in laryngology. Oertel is credited with the first clinical examination of the larynx with a stroboscope in 1878.¹ His primitive system employed a rotating perforated disc and laryngeal mirror to intermittently illuminate the glottis. Modern stroboscopes, while expensive, are considerably less cumbersome and have gained widespread use, particularly in Japan and Europe.²

Much of the behavior of the vibrating vocal folds is not visible through indirect laryngoscopy. Because an image on the human retina persists for approximately 0.2 seconds, the vibrating vocal folds appear as a blur along their medial edge. Stroboscopy creates the illusion of slow motion by generating light flashes at a rate slightly out of synchrony (approximately 2 Hz) with the fundamental frequency of phonation. This transforms the duration of a typical laryngeal cycle from 5 milliseconds to somewhere between 0.25 and 1 second. The "cycle" therefore represents a montage of many laryngeal cycles, rather than documentation of a single cycle as in high-speed photography.

Stroboscopic analysis was instrumental in the development of the cover-body theory of Hirano and Kakita,³ which proposes that the stiff underlying body formed primarily by the vocalis muscle is responsible for the transverse movements of the vocal folds, while the looser mucosal cover vibrates primarily in the vertical dimension and forms a traveling mucosal wave.³ As confirmed through supraglottic and subglottic videostroboscopy, the vocal folds vibrate as an upper and a lower margin during phonation. The lower margins separate first, forming a subglottic vault filled with a small volume of air, which is released as a puff into the vocal tract. The lower margins then return to the midline, and a gradual closing of the upper margin follows. In unilateral paralysis, there is a loss of stiffness of the underlying body, reducing the distinction between the upper and lower margins and creating a diminution or loss of the traveling wave.⁴

In addition to its research value, stroboscopy has been used for decades in clinical laryngology. Von Leden⁵ emphasized the usefulness of stroboscopy in differentiating functional from anatomic laryngeal lesions, and for the early detection of invasive cancers of the vocal folds. However, stroboscopy is limited when aperiodicity, severe hoarseness, or breathlessness impairs its ability to synchronize the flashes accurately.²

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Presented at the meeting of the American Laryngological Association, Waikoloa, Hawaii, May 4-5, 1991.

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Previous research supported the widespread view that laryngeal paralysis is accompanied by a loss of the mucosal traveling wave on the paralyzed fold.² Schoenharl⁶ studied laryngeal paralysis with stroboscopy and found that in 55 of 62 cases the traveling wave was absent. The presence of the mucosal wave in patients with a paralyzed fold was interpreted as a sign of some degree of reinnervation, suggesting an improved prognosis for eventual complete recovery.^{2,7} Fex⁷ published a study in 1970 on the stroboscopy of laryngeal paralysis. He agreed with previous authors that in acute recurrent laryngeal nerve (RLN) paralysis the glottic wave is absent. The mucosal traveling wave was found to be an accurate reflection of thyroarytenoid muscle tonus, and its return indicated recovery of RLN function even when vocal fold abduction could not be detected.⁷ The possibility that the return of the traveling wave was promoted by vocal cord fibrosis was not discussed.

Isshiki et al⁸ published a detailed account of the effects of asymmetric vocal fold extension, using excised larynges and a computer model to assess the effect of unilateral changes of cricothyroid (CT) contraction and subsequent vocal fold stiffness. According to Isshiki et al, the vibratory findings produced by asymmetric laryngeal tension depend on the degree of glottic closure. They found that in simulated superior laryngeal nerve (SLN) paralysis the true vocal folds vibrated at the same frequency but out of phase, with the more tense fold (active CT) preceding the less tense one. This finding was later confirmed by Isshiki's group in a study performed on live dogs.⁹

Another study of canine laryngeal paralysis was performed by Moore et al⁴ employing videostroboscopy. The authors found that canine RLN paralysis produces a difference in the timing of the onset of vocal fold lateral displacement and loss of the normal two-mass laryngeal vibration. The mucosal wave was markedly diminished but not lost in RLN paralysis.⁴

The morphological findings in laryngeal paralysis, including the Wagner-Grossman theory of vocal fold position in RLN and vagal paralysis, can be appreciated through indirect laryngoscopy alone and will not be the focus of this research.

The purpose of this study is to update earlier analyses of asymmetric laryngeal vibration by using videostroboscopy. First, it will describe the stroboscopic appearance of the larynx in paralysis. Previous reports of vibrational findings in laryngeal paralysis have been limited by the difficulty in defining the actual type of paralysis. Temporary induced paraly-

sis was used in this study and provides a known site of lesion and the ability to compare laryngeal vibration before and after paralysis. Second, videostroboscopic images were synchronized with glottographic waveforms to more accurately assess the timing of glottic opening and closure on the glottographic waveforms. Third, an analysis of a clinical series of patients with various types of vocal fold paralysis was performed to verify that the findings noted in induced paralyzes are similar to those in a typical laryngology practice. Finally, asymmetric vibration of the laryngeal mucosa provides an opportunity to utilize recently developed techniques for the objective analysis of videostroboscopic images for the degree of vocal fold symmetry.

MATERIALS AND METHODS

Method of Paralysis Induction. Three adult male volunteers with a mean age of 36 years were studied in this experiment. The volunteers appeared normal on laryngeal examination and had no history of laryngeal disorders. Vocal fold paralysis was induced by infiltrating 2% lidocaine hydrochloride with a 25-gauge needle into the expected location of the nerve. The left RLN was infiltrated in the tracheoesophageal groove approximately 2 cm inferior to the cricoid cartilage. The left SLN was infiltrated as described by Abelson and Tucker.¹⁰ Ten cubic centimeters were necessary, with injection both at the posterior edge of the thyroid ala and inferiorly near its passage posterior to the thyrohyoid muscle. To create a combined ("vagal") paralysis, an SLN injection was performed, verified by stroboscopy, and immediately followed by an RLN injection. Subject 1 had SLN, RLN, and combined paralysis induced with lidocaine. Subject 2 had the RLN only injected, and subject 3 had the SLN only injected.

Videostroboscopic Analysis. The method of videostroboscopic analysis was modified from previous reports by Bless et al¹ and Kitzing.² Emphasis was placed in the analysis on the characteristics of the traveling mucosal wave. The onset, extent, and velocity of the traveling wave were analyzed and estimated by advancing the videotape frame by frame. Phase differences were noted in cases of asymmetric vibration. Other characteristics included the degree of glottic closure, the lateral excursion of the fold during vibration (termed amplitude by Bless et al¹), and the regularity of glottic cycles, reflecting the presence or absence of severe frequency perturbation.

Stroboscopy. The experimental equipment required for these studies is depicted in Fig 1. Stroboscopy was performed with a Bruel & Kjaer 4914A (Orange, Calif) stroboscope. A microphone (Sennheiser MD

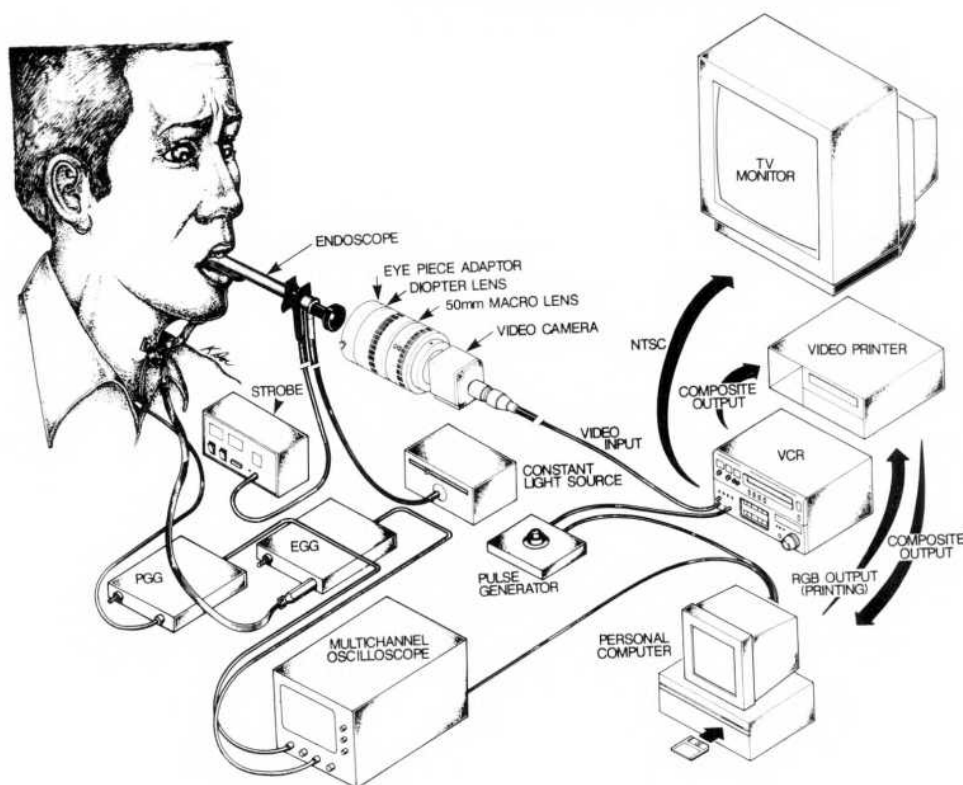


Fig 1. Experimental setup for recording of videostroboscopic images and concurrent glottographic waveforms. Computer includes Frame Grabber hardware, which allows digitization of videostroboscopic images, and Image Pro software for analysis of images.

4026) transduced the speech signal to allow synchronization with the video images. A Toshiba Charge Coupled Device (CCD) color video camera (model 1K-C30A, Buffalo Grove, Ill) imaged the glottis. The images were recorded onto a $\frac{3}{4}$ -in professional videocassette recorder (Sony VO-9850, Teaneck, NJ) equipped with a time coder. Still images from the videotape were made with a color video printer (Sony Mavigraph, Teaneck, NJ).

Glottography. Videostroboscopy and glottography were performed simultaneously during phonation of the vowel /i/ produced at a constant pitch and loudness. Transduction of photoglottography (PGG) waveforms required constant illumination of the larynx with a miniature light source (Karl Storz 481-C, Culver City, Calif) in addition to the stroboscopic light source. A 90° telescope (Wolfe, Rosemont, Ill) with two light inputs was used to visualize the glottis. Light transmission for PGG waveforms was transduced with a photosensor (Centronics OSD 50-2, Mountainside, NJ) held in position on the skin overlying the CT membrane. Electroglottography (EGG) recording electrodes were strapped into position onto the subject's neck, overlying the thyroid lamina at the level of the true vocal folds. A Synchrovoice electroglottograph (Harrison, NJ) recorded the EGG waveforms.

Synchronization. Videostroboscopic images were correlated with glottographic signals to provide pre-

liminary information about the timing of events in laryngeal paralysis. Further details about the synchronization method are being published in a separate report from this laboratory.¹¹ Briefly, a 5-millisecond square wave pulse was digitized and simultaneously recorded on the audio channel by the videotape recorder. By correlating the 5-millisecond square wave pulse with the vertical synchronization trace of the video signal, the position on the glottographic waveform could be precisely correlated with individual video images. A Hitachi oscilloscope (model V-1050 F, Torrance, Calif) was used to extract the vertical trace of the video signal for recording.

Electroglottography, photoglottography, synchronizing pulse and vertical trace of the video signal were digitized via a Labmaster 12-bit analog-to-digital board housed in an IBM compatible computer. The EGG and PGG signals were verified on a Tektronix 5116 (Beaverton, Ore) storage oscilloscope prior to recording. The waveforms were analyzed by using a commercially available software package for the PC system (C-Speech, Paul Milenkovic, University of Wisconsin, Madison, Wis).

Videostroboscopic Image Evaluation. Images were analyzed by using an image processing software package previously described¹² (Image Pro II, Media Cybernetics, Silver Spring, Md). The hardware necessary for image analysis included a Frame Grabber to digitize and analyze video images (Data Transla-

TABLE 1. SUMMARY OF STROBOSCOPIC EVALUATION OF LIDOCAINE-INDUCED LARYNGEAL PARALYSIS

Subject	Site	Regularity*	Closure	Symmetry of Vibration and Characteristics of Mucosal Wave
1	SLN	Regular	Complete	Moderate asymmetry of TW; greater velocity and excursion of TW on normal side, particularly at low frequency of vibration; decreased tension of TVF on injected side; occasional shifting of glottis from side to side during vibration
1	SLN + RLN	Variable aperiodicity	Small posterior glottic chink	TVFs vibrated at different level during portions of cycle (Fig 3C); profound asymmetry of TW (Fig 3); normal TVF crossed midline during vibration; TW velocity and excursion greater on normal side; loss of TVF tension; TVF higher on normal side
1	RLN	Regular	Variable	Marked diminution of TW excursion and velocity on side of injection; greater TVF excursion on normal side (see symmetry ratio, Fig 4A)
1	RLN paresis	Regular	Complete	Asymmetry of vibration with greater excursion and velocity of TW on normal side; normal TVF adduction and abduction
2	RLN	Variable aperiodicity	Large chink	Marked asymmetry of TW (Fig 2B); greater velocity of TW on normal side; vibration out of phase; normal TVF precedes paralyzed TVF
3	SLN	Regular	Complete	Diminished mucosal wave on side of paralysis; flaccidity of TVF on injected side

SLN — superior laryngeal nerve, RLN — recurrent laryngeal nerve, TW — traveling wave, TVF — true vocal fold.

*Regularity indicates ability of subject to maintain constant frequency and therefore facilitate stroboscopy. High jitter (frequency perturbation) results in irregular vibration and difficulty in analyzing glottic wave.

tion, DT-2853 60SQ, Marlboro, Mass). The desired portion of the video image can be outlined by use of a pointing device, and then the area of the trace or the length of a line is calculated by and expressed in pixel units by the software.

Images were digitized from the most closed and most open portions of the vocal cycle, and the width of the vocal folds was measured during these intervals. A measure was then computed of the symmetry ratio, which expresses the excursion of one vocal fold in proportion to that of the other fold. Symmetric vibratory movement is marked by an equal excursion of both vocal folds from the midline during phonation. When the lateral motion of one fold is markedly reduced, as in unilateral RLN paralysis, the symmetry ratio approaches zero. Further details regarding the objective analysis of videostroboscopic images have been recently published by Sercarz et al.¹²

Chronic Paralysis Study. We reviewed the videotapes and clinical files of all patients with a diagnosis of vocal fold paralysis evaluated in the UCLA Voice Laboratory during the years 1988 to 1991. Patients were excluded if the paralysis had been previously treated or if inadequate videotape or clinical information was available. All patients underwent stroboscopy and glottographic (PGG and EGG) recordings. In each case, medical records were analyzed to determine the probable site of the paralysis. Three cases of vagal paralysis had documented sites of lesion. Two patients had laryngeal paralysis following penetrating trauma to the skull base and subsequent high vagal paralysis. The third had undergone a tumor with sacrifice of cranial nerve X at the skull base.

Two clinical cases were diagnosed as SLN paralysis. One patient developed a dysphonia following thyroid surgery marked by a reduced ability to modulate pitch and vocal fatigue. Later exploration revealed a lack of function of the SLN on direct nerve stimulation. Another patient suffered neck trauma and developed a dysphonia marked by abnormal laryngeal vibration and normal vocal fold abduction and adduction. In the latter patient, there was a rotation of the posterior commissure in the direction of the paralysis side.

Fifteen additional patients received diagnoses of unilateral RLN paralysis based on history and indirect laryngeal examination.

RESULTS

Induced Paralysis. The three subjects underwent stroboscopy prior to induction of paralysis. In each case, vibration was normal with equivalent velocity and excursion of the traveling wave and symmetric tension of the vocal folds bilaterally. Closure was complete in each case.

In each case of SLN paralysis, the volunteer reported anesthesia of the larynx and an inability to sing at a high pitch in addition to the findings described.

Table 1 summarizes the videostroboscopic findings in induced vocal fold paralysis. Following RLN injection, the vocal process on the paralyzed side remained in the paramedian position. There was no rotation of the posterior glottis that was appreciable in any of the induced paralysis states.

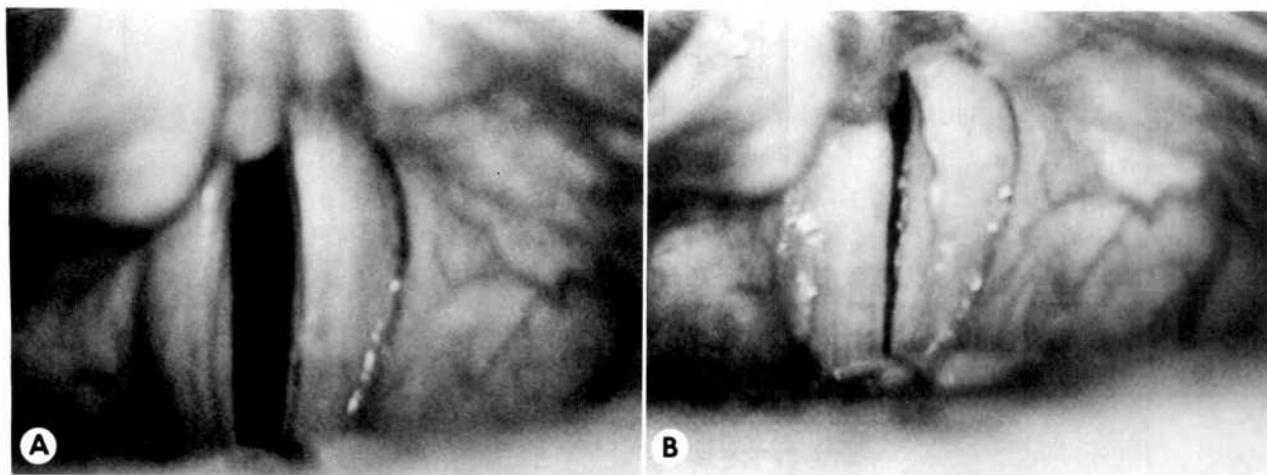


Fig 2. (Subject 2) A) Normal phonation, showing symmetric traveling mucosal wave. B) Following left recurrent laryngeal nerve injection. Right mucosal wave has completed its vibration. Wave of lesser excursion is now traveling along left (paralyzed) vocal fold.

The most consistent finding in each case of induced paralysis was a diminution of traveling wave velocity and less lateral excursion on the side of the injection, whether SLN, RLN, or combined. Although the traveling wave was attenuated in each case on the side of the paralysis, the wave was observed during each trial. For subject 1, who under-

went all three types of paralysis, the traveling wave asymmetry was greatest in the vagal paralysis, followed by RLN and SLN in that order.

Figure 2A is normal phonation from subject 2 with a symmetric traveling wave. Figure 2B, following left RLN injection, demonstrates asymmetric vibra-

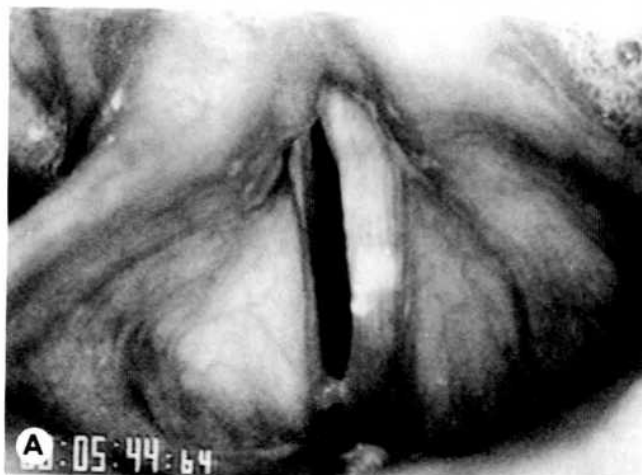
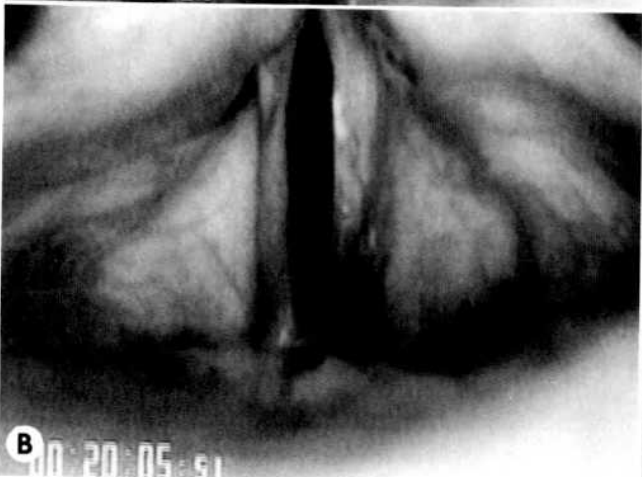


Fig 3. (Subject 1) Portions of glottic cycle following injection of superior and recurrent laryngeal nerves. A) Midcycle, with brisk lateral motion of right (normal) vocal fold, without visible vibration of paralyzed fold. B) Later in cycle, markedly attenuated wave traverses left, paralyzed fold. C) Normal fold, having completed its vibration, returns to position just past midline, at level higher than paralyzed left fold.



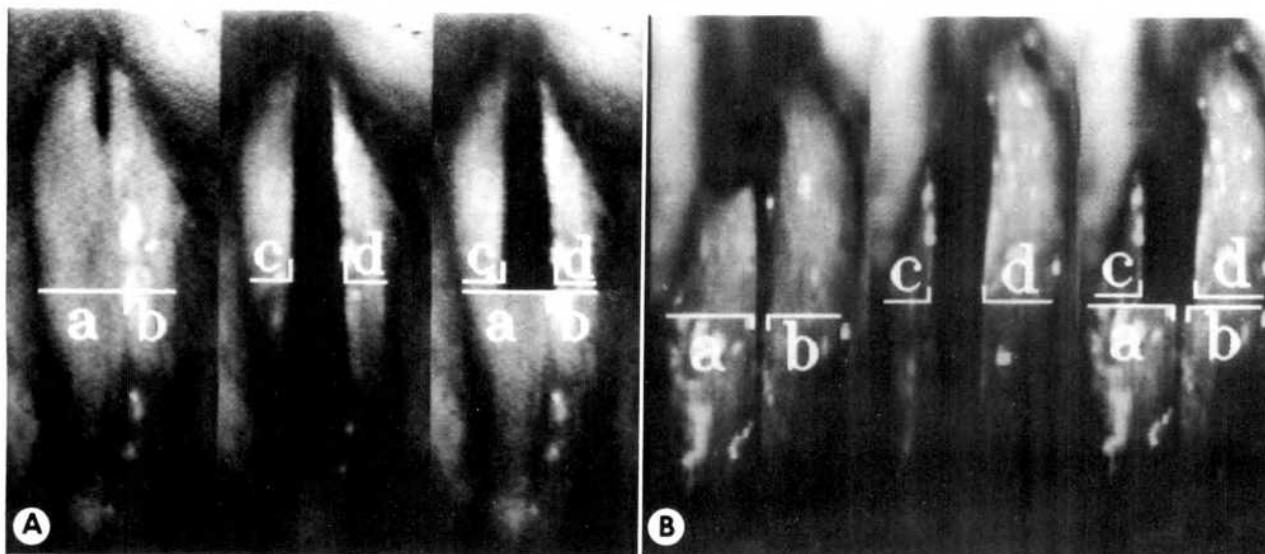


Fig 4. Symmetry ratio for two volunteers with induced recurrent laryngeal nerve paralysis (see text). A) Subject 1. B) Subject 2.

tion. The normal (right) vocal fold has completed its vibration, and the paralyzed (left) fold is shown with an attenuated traveling wave. Figure 3 is a series of still video frames from subject 1 with a left combined RLN and SLN paralysis. Figure 3A is early in the glottic cycle, with a vigorous excursion of the uninjected (right) vocal fold. Later in the glottic cycle, a minimal mucosal wave is seen on the left vocal fold (Fig 3B). Finally, the right vocal fold, positioned at a higher level than the paralyzed left vocal fold, crosses the midline, and the glottis closes (Fig 3C).

Figure 4 depicts measurement of the symmetry ratio for subjects 1 and 2 following RLN injection. The lengths *a* and *b* (most closed portion of the glottal cycle) and *c* and *d* (most open) represent the width of the right and left vocal folds. The calculated symmetry ratio for subject 1 was 0.139 (Fig 4A) and for subject 2 was 0.151 (Fig 4B). In a perfectly symmetric case, the ratio is 1.0, and in a case with no lateral vocal fold movement in one of the folds the ratio is 0.

Figure 5 demonstrates the results of synchronizing the glottographic signal to the videostroboscopic image from subject 1 following RLN injection. Figure 5A is a stroboscopic image taken immediately following opening of the glottis. Figure 5B is the synchronized glottography. There is an upward deflection in the differentiated EGG (dEGG) waveform that correlates well with the onset of vocal fold opening. Figure 5C,D is synchronized from a point at midcycle. Figure 5E,F is from an image immediately preceding the point of glottic closure. The downward deflection in the dEGG waveform closely correlated with the instant of laryngeal closure. Similar findings are documented in Fig 6, which shows the results of

synchronizing strobe images and glottography in subject 1 with SLN paralysis at the moment of opening (Fig 6A,B) and closure (Fig 6C,D). Again, the timing of opening and closure of the vocal folds is predicted by the dEGG waveform.

Clinical Cases. The results of a series of 20 consecutive patients analyzed at the UCLA Voice Laboratory will now be described. Of the 15 RLN patients, 3 could not be included because aperiodic vibration or a large glottic gap prevented analysis of the mucosal traveling wave. The results of the 12 remaining patients with unilateral RLN paralysis and adequate stroboscopy are summarized in Table 2. Ten of 12 patients had a mucosal wave present on the paralysis side. The wave asymmetry was similar to that observed in the induced paralysis: the normal wave had a greater velocity and traveled farther along the vocal fold mucosa. There was a phase shift, with the normal side vibrating sooner than the side of the paralysis. The asymmetry was marked in the majority of patients with unilateral RLN paralysis.

The findings in the two patients with SLN paralysis parallel those in the group with induced paralysis. There was normal abduction and adduction of the vocal folds in both cases. Glottic closure and regularity (lack of noticeable frequency perturbation) were normal. Analysis of the mucosal wave revealed mild to moderate asymmetry of the traveling wave. On the normal (nonparalysis) side, the wave appeared earlier, had a greater velocity, and traveled farther along the surface of the vocal cord mucosa.

The mucosal wave findings in vagal paralysis are similar to those in RLN paralysis. Only one of the three patients had the frequently cited finding of rotation of the posterior glottis in the direction of the

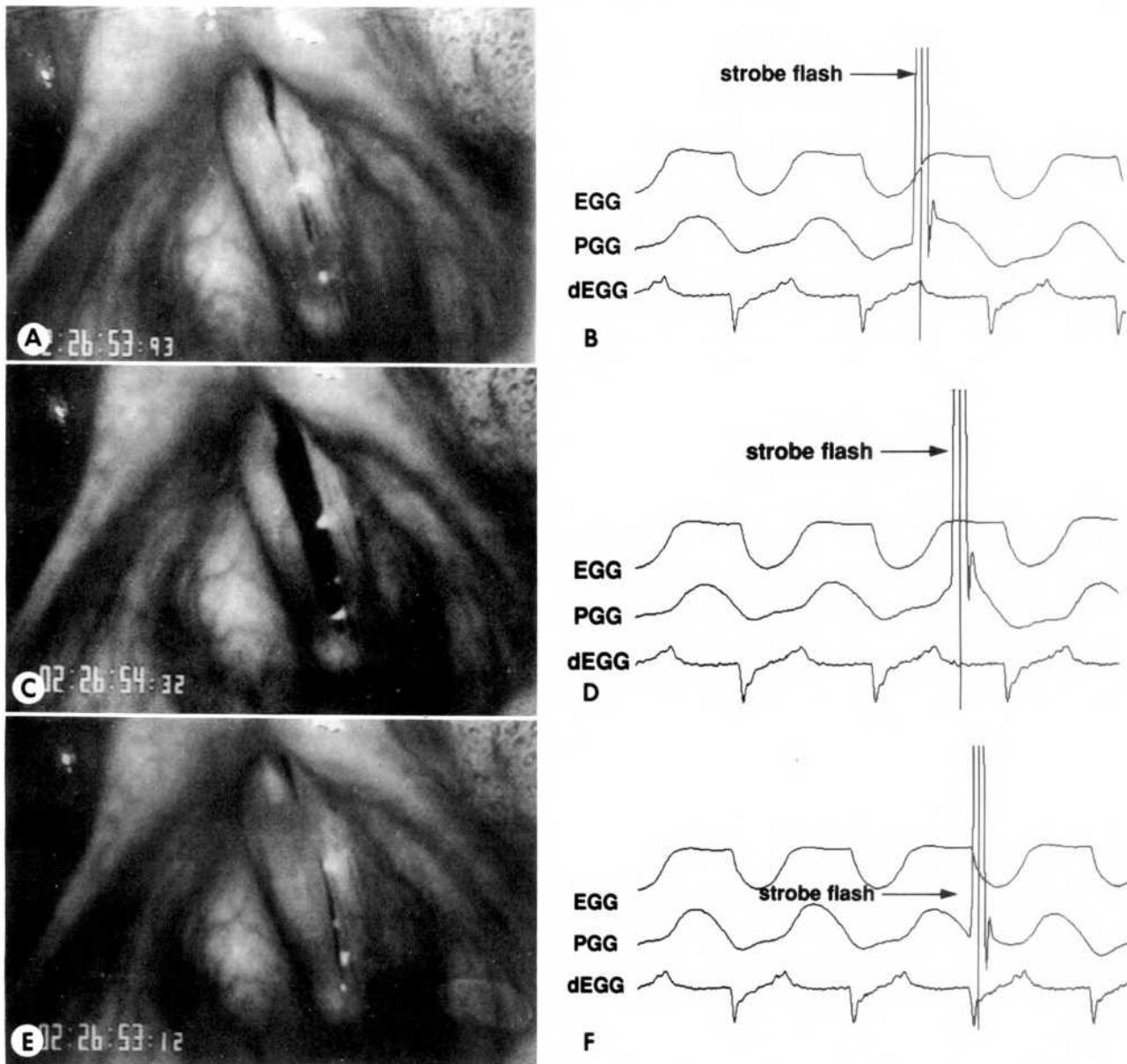


Fig 5. (Subject 1) Correlation of glottographic information with stroboscopic images in recurrent laryngeal nerve paralysis. EGG — electroglottography, PGG — photoglottography, dEGG — differentiated EGG. A) Immediately following vocal fold opening. B) Corresponding glottographic waveforms, with strobe flash occurring just after positive deflection in dEGG waveform. C) Later in cycle, at mid-opening. D) Glottographic waveforms, with strobe occurring near peak of PGG waveform. E) Image of glottis at point of closure. F) Corresponding waveforms; nadir of dEGG waveform corresponds to strobe flash.

paralysis. In one of the patients with vagal paralysis, the glottic gap was wide throughout the cycle and there was very irregular vibration of the mucosal wave bilaterally. The other two patients had marked asymmetry of the traveling wave, vibration out of phase, and differences in the velocity and excursion of the traveling wave similar to those found with induced vagal paralysis in this study.

DISCUSSION

There are several advantages of studying induced vocal fold paralysis stroboscopically. Temporary

chemical paralysis allows comparison with normal stroboscopy in the same individual. It also provides an opportunity to study recovering RLN weakness and observe the gradual recovery of symmetry, as in the study of vocal fold paresis in subject 1. Before discussing the stroboscopic findings in particular paralytic states, we will review the overall relationship between tension of the vocal fold and vibratory characteristics.

Unlike previous studies^{2,6,7,13} of stroboscopy in vocal cord paralysis, the data in the present report indicate that the mucosal wave is always *affected* but

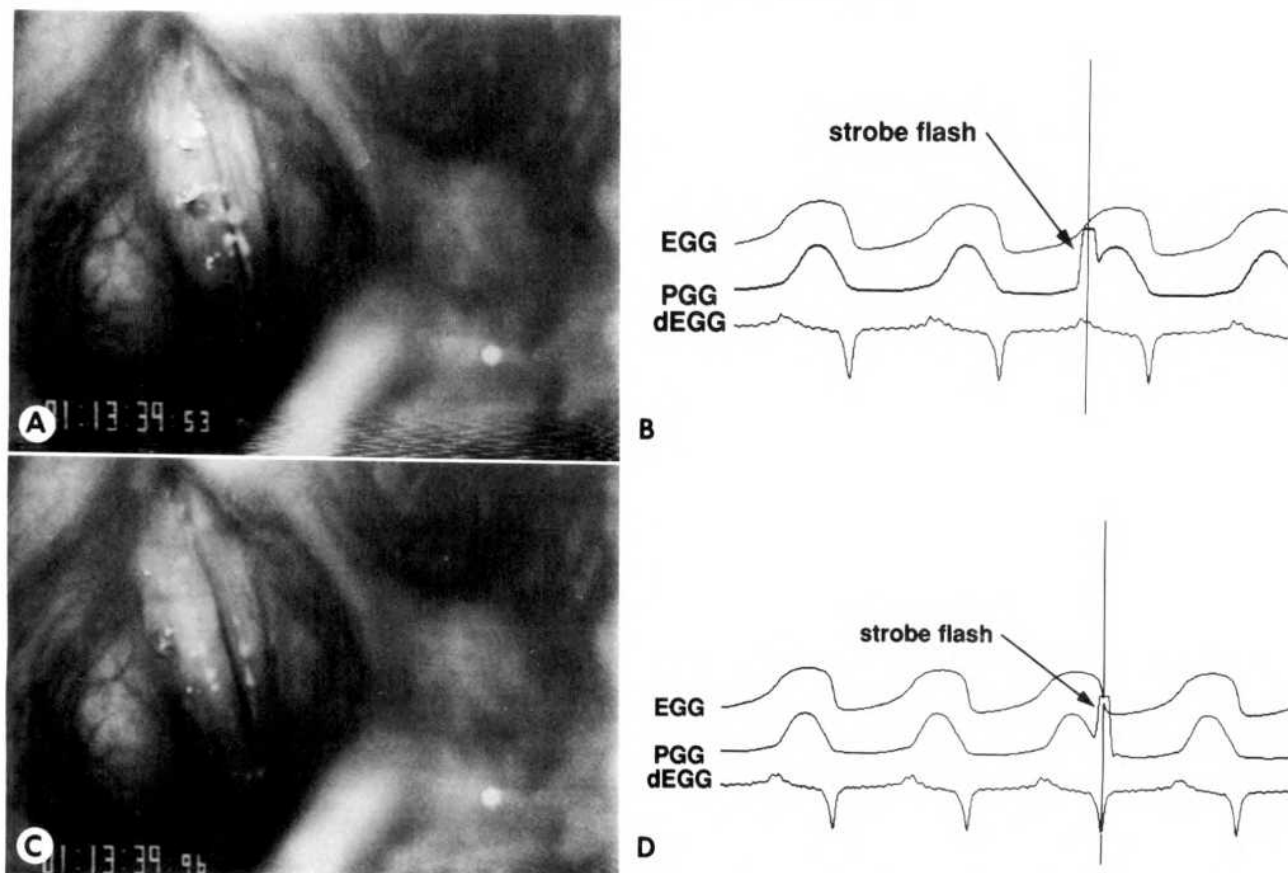


Fig 6. (Subject 1) Correlation of glottographic information with stroboscopic images in superior laryngeal nerve paralysis. Abbreviations as in Fig 5. A) Immediately following vocal fold opening. B) Corresponding glottographic waveforms, with strobe flash occurring just after positive deflection in dEGG waveform. C) At point of closure of glottis. D) Corresponding glottographic waveforms, with strobe again occurring at nadir of dEGG waveform.

not invariably *absent* in RLN and vagal paralysis. All patients with laryngeal paralysis of any type, experimental or clinical, had an unambiguous asymmetry of laryngeal vibration demonstrated stroboscopically. Furthermore, the data presented indicate that the asymmetry follows a pattern: the normal vocal fold traveling wave has a greater velocity than that of the paralyzed fold, is observed earlier in the glottic cycle, and traverses farther over the surface of the vocal fold mucosa. The symmetry ratio data were presented to document the greater excursion of the vocal fold margin on the nonparalyzed side during the most open portion of the cycle in unilateral RLN paralysis.

The findings described here are similar to those reported by Tanabe et al⁹ in a report on asymmetric glottic vibration studied in canine larynges. It is not surprising that there was a visible difference in the velocity of the traveling waves on two vocal folds. Basic research on the propagation of waves in elastic media have indicated that there is a direct relationship between the stiffness of the material or reactance to deformation and the velocity of a harmonic traveling wave.¹⁴ The lack of thyroarytenoid stiffness and/or CT contraction is probably the central cause of the

vibratory differences in laryngeal paralysis. In a morphologic study of the vocal fold as a vibrator, Hirano¹⁵ stated that the CT and thyroarytenoid muscles had the greatest effect on the stiffness relationship between the body and the cover of the vocal fold; this finding may explain why either muscle may elicit similar changes in the traveling wave velocity and excursion.

For the two patients with absent glottic waves, each had poor glottic closure that reduced the degree of vocal fold contact. This tended to decrease the ability of stroboscopy to detect the very subtle mucosal wave that generally occurs on the paralyzed vocal fold.

Because of its sensitivity in demonstrating slight differences in vocal fold vibration, stroboscopy is particularly useful in the study of laryngeal paralysis. In subtle cases, such as RLN paresis or isolated SLN paralysis, an abnormality of traveling wave motion may be the easiest finding to elicit. The results of this study suggest that traveling wave asymmetry may be one of the most salient observations to make in suspected paralysis, because traveling wave asymmetry

TABLE 2. RESULTS OF PATIENTS WITH RECURRENT LARYNGEAL NERVE PARALYSIS

	No. of Patients
Glottic closure	
Complete	2
Mild to moderate incomplete closure	5
Severely incomplete closure	5
Glottic wave: extent of wave excursion along vocal fold mucosa	
Symmetric	0
Mild to moderate asymmetry	2
Marked asymmetry	8
Absent on paralysis side	2
Glottic wave: estimated speed of glottic wave	
Symmetric	0
Greater velocity (earlier wave) on normal side	10
Greater velocity on paralyzed side	0
Absent wave on paralyzed side	2
Vocal fold lateral displacement during vibration*	
Equivalent	0
Mild to moderate asymmetry	4
Marked asymmetry	8
Of 15 patients with clinical diagnosis of recurrent laryngeal nerve paralysis, 12 had adequate regularity of vibration for suitable stroboscopy. Their results are presented here.	
*Lateral motion during vibration was invariably greater on side opposite paralysis (normal side). See Fig 4, showing symmetry ratio in induced paralysis.	

is a consistent finding in untreated laryngeal paralysis. In subject 1, traveling wave asymmetry was also identified in RLN paresis.

Despite this consistency, there is a significant variability of findings among different patients and even within the same individual phonating at two different fundamental frequencies. For example, in RLN paralysis, CT muscle contraction at high pitch adds vocal fold stiffness and tends to reduce the degree of asymmetry. One patient in the study developed RLN paralysis following thyroid surgery 20 years before the examination; the paralysis is still largely uncompensated. He apparently compensates with CT tension, producing speech at a high pitch level (paralytic falsetto) that provides glottic closure and only moderately asymmetric traveling wave motion.

Both RLN paralysis and combined SLN and RLN paralysis produced the above changes in the traveling wave. Although the combined paralysis was characterized by a greater degree of asymmetry and a more flaccid or "wavy" paralyzed cord, it is doubtful from our data whether stroboscopy alone can be of significant assistance in differentiating vagal from RLN paralysis.

Isolated SLN paralysis is a rarely noted clinical

entity that probably often goes undetected.^{10,16,17} The SLN provides sensation to the supraglottic larynx through its internal branch and motor fibers to the CT muscle via its external branch. The motor branch is in close proximity to the superior thyroid vessels and is therefore vulnerable to injury during thyroid surgery. According to Ward et al¹⁷ and other authors,¹⁰ paralysis of the CT muscle causes 1) lack of longitudinal tension of the true vocal folds, 2) a tilt of the larynx because of the downward motion of the contralateral intact CT muscle, and 3) a rotation of the posterior glottis toward the side of the paralysis because of the unopposed CT muscle's pulling the anterior thyroid cartilage toward the intact side.

Unfortunately for the clinician, as stated by Dedo in his study on experimental and clinical vocal fold paralysis, the expected findings in SLN paralysis "...are not consistent or obvious enough to be useful in clinically diagnosing superior laryngeal nerve paralysis."^{16(p1503)} Neither of the two volunteers undergoing SLN injection for this study had an unequivocal rotation of the posterior glottis toward the paralyzed side, as described in the literature. The asymmetry of the traveling wave, however, was easy to observe stroboscopically.

Although the SLN patients demonstrated that their folds were vibrating at the same frequency, there was a difference in velocity and a phase lag, with the nonparalyzed fold completing the vibratory cycle before the paralyzed fold. This finding has been previously reported in both live dogs and excised larynges.^{8,9} Similar asymmetry occurred, although to a greater degree, in the present study in RLN paralysis.

It is possible that the expected rotation of the posterior glottis was too subtle to be appreciated in these patients. In a canine study, the glottic rotation following unilateral CT paralysis was only 3.5° to 17°.⁹ At the lower end of this range, the rotation probably is imperceptible.

Following SLN injection, the asymmetric vibration and morphology, supraglottic anesthesia, and inability to sing at a high pitch produced a constellation of findings consistent only with SLN paralysis, in the opinion of the authors. It is difficult to prove complete SLN paralysis, however, even if a loss of CT activity is documented on electromyography. It is possible, but unlikely, that there is another explanation for the stroboscopic findings.

Clinical correlation is required in the diagnosis of an isolated SLN paralysis with stroboscopy. Other possible causes of asymmetric laryngeal vibration should be considered, including scarring or a submu-

cosal mass, which could rarely produce a similar stroboscopic picture.^{2,18} In the setting of suspected SLN injury — for example, a postthyroidectomy patient with a loss of the ability to sing or modulate pitch in continuous speech — an asymmetric mucosal traveling wave or asymmetric vocal fold excursion suggests SLN paralysis, even if other characteristics such as posterior glottic rotation or tension asymmetry are not observed on indirect laryngoscopy alone. In such a situation, laryngeal electromyography provides a sensitive method to verify the presence of a paralysis.¹⁹

A method of synchronizing glottographic waveforms with videostroboscopic images has recently been developed in our laboratory.¹¹ Figures 5 and 6 indicate that in studies of patients with asymmetric laryngeal vibration, the first derivative of the EGG waveform provides information about the timing of laryngeal opening and closure, provided that adequate vocal fold contact occurs during phonation. The upward deflection in the EGG first-derivative waveform is a good indicator of the moment of opening, whether in normal patients or in those with asymmetric vibration. The nadir of the dEGG waveform has previously been shown to closely correspond to the moment of laryngeal closure.^{20,21} The largest positive peak in the dEGG waveform has been shown to correlate with opening.²⁰ Our data from synchronizing the videostroboscopic images with glottographic waveforms (Figs 5 and 6) indicate that a similar relationship exists in both RLN and SLN paralyses. Childers et al²⁰ noted that there was a significant variation in dEGG waveforms dependent on the experimental conditions, such as frequency, which somewhat limits the accuracy of estimating glottic events based on dEGG.

Computerized digital analysis of stroboscopic images holds the promise for quantifying traveling wave abnormalities associated with laryngeal disorders. Figure 4 demonstrates the symmetry ratio applied to laryngeal paralysis. The ratios can provide an objective measure, allowing interpatient and intrapatient comparisons of asymmetry.

Although this study did not report data describing the results of reinnervation or treatment on videostroboscopic findings in RLN paralysis, stroboscopy can document a return of normal symmetry of laryngeal vibration, particularly when the thyroarytenoid muscle is reinnervated. Crumley²² recently updated his experience with ansa hypoglossi nerve transfer for the treatment of unilateral vocal fold paralysis. He used stroboscopic analysis to document reinnervation, observing return to symmetric vibration in four of five patients assessed following reinnervation.²²

In conclusion, stroboscopy is a useful tool in the evaluation of patients with suspected laryngeal paralysis. Paralysis of the SLN, RLN, or both results in asymmetric laryngeal vibration that is easily identified even by inexperienced observers. The mucosal wave has a greater velocity and travels further along the mucosa on the normal fold. The probable cause of these vibratory findings is the reduced stiffness in the paralyzed cord, which reduces the velocity and extent of the traveling mucosal wave. Stroboscopy can identify abnormal vibration in patients with otherwise normal findings on indirect examination. Our early experience suggests that stroboscopy cannot reliably distinguish RLN paralysis from vagal paralysis. Studies are being planned in the canine model to better quantify the traveling wave findings in laryngeal paralysis.

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NONINVASIVE TECHNIQUE FOR ESTIMATING SUBGLOTTIC PRESSURE AND LARYNGEAL EFFICIENCY

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The clinical assessment of aerodynamic parameters is important in the physiology and pathophysiology of laryngeal function. Vocal efficiency is among these objective measurements and can be calculated from simultaneous recordings of subglottic pressure, airflow, and sound intensity. Modern techniques allow us to accurately determine sound intensity and airflow. However, methods to determine subglottic pressure are either invasive or laborious. We have evaluated a noninvasive, indirect method to determine subglottic pressure by using a technique based on the interruption of transglottic airflow during phonation. The correlation between the indirectly acquired subglottic pressure measured in the oral cavity by using this technique and the subglottic pressure obtained directly by translaryngeal puncture in human volunteers was highly significant in 35 trials ($r = .92$, $p < .01$). This study describes a reliable technique for the noninvasive measurement of subglottic pressure, sound intensity, and airflow.

KEY WORDS — subglottic pressure, vocal efficiency, vocal physiology, voice production measurement.

INTRODUCTION

Clinical assessment of aerodynamic parameters at the larynx is essential to obtaining an understanding of the physiology and pathophysiology of voice production. The larynx acts as a transducer, converting aerodynamic power from the lungs into acoustic power. The efficiency of this conversion is one of several objective measurements of laryngeal function. It can be expressed by the ratio of acoustic power (sound intensity) to aerodynamic power (subglottic pressure multiplied by airflow).¹

Modern techniques allow us to determine airflow and sound intensity accurately. However, it is more cumbersome to assess subglottic pressure. The following methods are available.

1. Percutaneous catheter: a needle or catheter, to which a pressure transducer is connected, is placed through the cricothyroid membrane into the subglottis. This direct technique accurately measures subglottic pressure. However, it is invasive, is uncomfortable to the subject, and exposes him or her to certain risks involved with catheter placement.

2. Translaryngeal catheter: a small transducer or a catheter attached to a transducer is placed across the anesthetized larynx from the nasopharynx. The catheter itself and the anesthesia of the mucosa interfere with normal phonation, thereby potentially affecting the accuracy of this technique.

3. Intraesophageal catheter: the subject swallows

an air balloon attached to a tube. The pressure inside the balloon is recorded through the tube. The subglottic pressure is calculated from esophageal pressure when lung volumes are held constant.^{2,3} This is time-consuming because it is necessary to record lung volumes and perform elaborate calibrations when body plethysmography is used.

All of these methods are invasive and pose significant logistical problems in a clinical setting. An alternative noninvasive technique has been developed for routine clinical measurement of subglottic pressure.^{4,5} This technique (the airway interruption method) was adapted from methods used to measure alveolar pressure in pulmonary laboratories.⁶ Its conceptual development is based in general fluid dynamics theory, which states that estimation of upstream pressure-flow relationships can be made by downstream pressure-flow measurements under certain conditions. Application of this theory to the air-filled phonatory system implies that under certain conditions, measurements obtained at the mouth can be used to estimate laryngeal pressure-flow relationships.⁵

One of these conditions is met during the closure period of voiceless stops.⁷ When the airstream of a vowel is interrupted by the closure of the lips, the glottis is open and translaryngeal pressure equilibrates with oral cavity pressure. Using this concept, Smitheran and Hixon⁵ developed utterances that met this condition in a clinical setting. Subjects were asked to phonate the syllable /pi/ in one train of

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Presented at the meeting of the American Laryngological Association, Waikoloa, Hawaii, May 4-5, 1991.

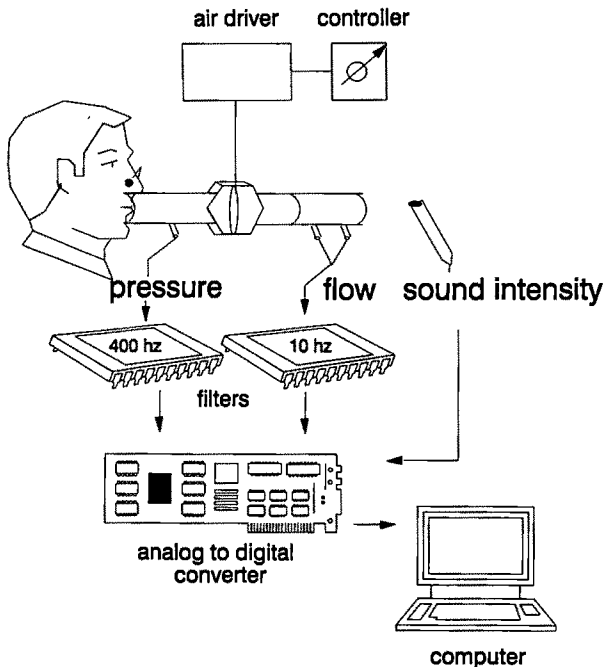


Fig 1. Schematic diagram of device used in this study.

several repetitions. Pressure in the oral cavity was measured during the closure period (/p/). Airflow was measured during the open period (/i/). Interpolation of the oral pressure during the closed phase was taken to represent prevailing subglottic pressure during the open phase when airflow was measured. Löfqvist et al⁸ showed that this indirect technique closely estimates subglottic pressure ($r = .92$).

Using a similar concept, Sawashima et al⁶ developed a tubular device that measures airflow, subglottic pressure, and sound intensity. With the mouthpiece held tightly at the lips, a mechanical shutter was used to interrupt the airflow during vowel production. The period when the shutter was closed is analogous to the closure period (/p/) in the preceding study.

The purpose of this study was to develop a similar device that could be used noninvasively to measure airflow, sound intensity, subglottic pressure, and frequency. Instead of a shutter, an air-driven balloon occluder was used. The resonance characteristics of the device were determined to correct the sound intensity calculations. This device can be constructed readily and provides a reliable way to calculate vocal efficiency and other aerodynamic parameters.

MATERIALS AND METHODS

Device. A schematic diagram of the device is shown in Fig 1. A disposable cardboard mouthpiece was attached to the balloon valve (Hans Rudolph inflatable balloon type 8250). A catheter attached to

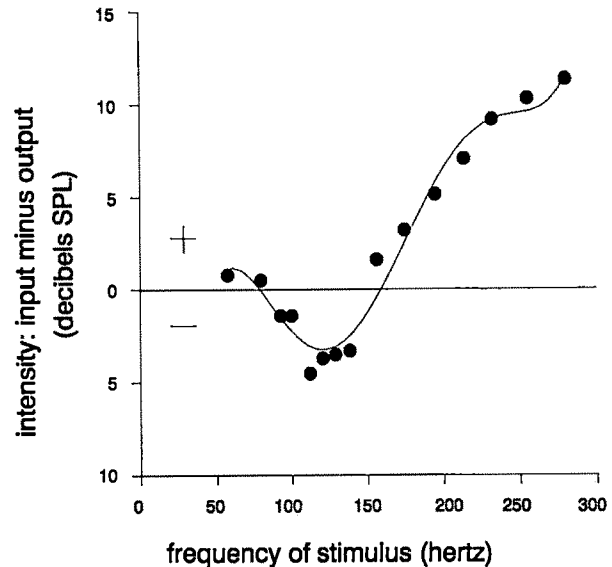


Fig 2. Sound intensity alteration of device as function of frequency. Value derived from y axis was added to measured sound intensity to correct for resonance characteristics of device at given fundamental frequency of sound source.

a pressure transducer (Celesco 0 to 10 cm H₂O, model LCVR) was connected between the mouthpiece and the balloon. A Fleisch-type pneumotachometer attached to a differential pressure transducer (Celesco 0 to 2 cm H₂O, model LCVR) was connected to the device distal to the balloon. The microphone of a Larson-Davis sound level meter was attached at the opening of the pneumotachometer. The balloon was connected to an automatic controller (Hans Rudolph controller 2430 series). The driver was regulated by a hand-held device that is able to vary the duration of balloon closure. The balloon valve, pneumotachometer, and microphone were attached to a hard plastic frame connected to a handpiece.

Sound Intensity Calculation. The sound from the end of the flowmeter was assumed to emanate in the fashion of a pulsating hemisphere. The microphone was attached 1 cm from the source and out of the airstream. Thus, intensity at the opening of the device (watts) was calculated to be

$$I = 10^{\text{dB SPL}/10} \times 10^{-12} (\text{W/m}^2) \times 2 \times \pi \times R^2$$

where R is the distance (meters) of the microphone to the sound source and dB SPL (decibels sound pressure level) is the sound intensity at the microphone. To calculate the intensity attenuation of the device, a sound source of known intensity was placed at the mouthpiece. The intensity of the sound output at the mouthpiece was measured. A correction factor (sound input minus output) for different frequencies was calculated and plotted as a function of frequency (Fig 2). A fifth-degree polynomial equation was fitted to

the curve. Subsequent intensity measurements were corrected during data analysis by using this equation.

The frequency of the sound source was derived from the pressure curve. In preliminary trials, the high-speed component of the pressure tracing was compared to the simultaneously acquired electroglottographic signal of a subject's phonation. The fundamental frequency of both curves was found to be the same. Computer-assisted frequency calculation of the high-speed component of the pressure tracing was therefore used in determining the intensity correction factor.

Data Acquisition. The signals from the pressure transducer were low-pass-filtered at 400 Hz, and those from the airflow transducer were filtered at 10 Hz. The analog signals from the transducers and the output from the sound intensity meter were digitized at 500 Hz by using an analog to digital converter. ASYSTANT II software was used to sample and analyze the data. Signals were acquired for 10-second periods and saved for later analysis.

Calibration. The pressure transducers were calibrated with a water manometer ($300 \text{ Pa} = 2 \text{ V}$). Airflow was calibrated with a Lab Crest airflow meter ($100 \text{ mL/s} = 1 \text{ V}$). Sound intensity was calibrated according to manufacturer instructions (Larson-Davis) by using a sound source specifically designed for this purpose.

Subjects. Six male and three female volunteers were used in this study. Ages ranged from 26 to 42 years (mean = 32). The subjects denied any history of smoking, laryngeal trauma or surgery, recent upper respiratory tract infection, or recent intubations. A total of 285 data points was obtained from the nine subjects.

Trials. Each subject was asked to place his or her mouth tightly around the mouthpiece. A nose clip was used to stop any air from escaping from the nares. The subjects were instructed to phonate /i/ into the device. They were instructed to maintain a constant pitch and intensity and not to push against the balloon when it was closed. Data were acquired at different pitches and intensities within the chest register. At random intervals during the phonation, the balloon was closed for 150 milliseconds. The optimal duration of the closure period was determined in preliminary trials.

Subglottic Pressure Measurement. In two male volunteers, percutaneous subglottic pressure was simultaneously recorded as well. Subglottic pressure was measured by using an 18-gauge needle placed through the cricothyroid membrane. The needle was

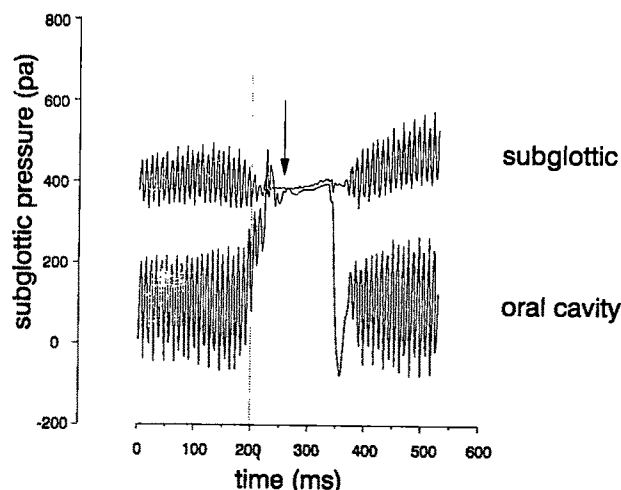


Fig 3. Representative sample of subglottic and oral cavity pressure. Airstream is occluded at 200-millisecond mark. When airflow is zero and vocal cords are in open position, as demonstrated by lack of oscillations, oral cavity pressure is equal to subglottic pressure.

attached to a pressure transducer (Celesco 0 to 10 cm H₂O, model LCVR). The signals were digitized and sampled at 500 Hz. During this part of the experiment, no filter was used for either the subglottic or oral cavity pressure signals. Thirty-five data points were obtained.

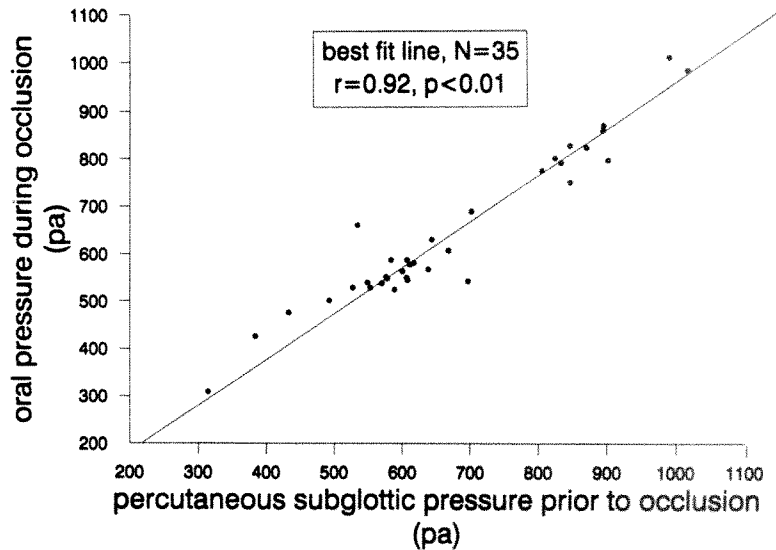
RESULTS

Figure 3 shows the relationship between percutaneous subglottic pressure and oral cavity pressure. At the start of the plateau it is evident that these two pressures are almost the same. The correlation between subglottic pressure prior to occlusion and oral cavity pressure during occlusion was high (Fig 4). A representative example of airflow, intensity, and pressure is shown in Fig 5. Average airflow, sound intensity, and fundamental frequency and the intensity correction factor based on fundamental frequency were calculated during the segment prior to occlusion. Subglottic pressure was determined at the beginning of the plateau of the pressure curve during occlusion, which is shown by the arrow. The Table shows the averages and ranges of pressure, airflow, sound intensity, and laryngeal efficiency in 285 trials in nine subjects.

DISCUSSION

The measurement of aerodynamic parameters is important when studying the physiology and pathophysiology of the larynx. Vocal efficiency, one objective measure of laryngeal function, is determined from simultaneous measurements of airflow, sound intensity, and subglottic pressure. It has been used as part of a battery of clinical tests to assess the effec-

Fig 4. Subglottic pressure prior to occlusion (open phase) versus oral cavity pressure during occlusion (closed phase) in 35 trials in two subjects.



tiveness of therapy in a variety of voice disorders. Readily available methods allow for determination of airflow and sound intensity. However, subglottic pressure is more difficult to obtain because many of the techniques are invasive, require elaborate calibration, or interfere with the normal vibratory characteristics of the larynx. For this reason, we investigated a noninvasive technique to measure subglottic pressure, airflow, sound intensity, and frequency simultaneously.

The results of this study validate the premise of the airway interruption technique: the pressure obtained during the closed phase represents prevailing translaryngeal pressure during the open phase. It was shown that the oral cavity pressure during airway interrup-

tion highly correlated with percutaneous subglottic pressure during phonation. Thus, this method provides an accurate and reliable way to determine subglottic pressure indirectly.

Airflow and sound intensity are also measured by the device investigated in this study. The values correspond well with those in the literature. In his thesis about vocal efficiency, Schutte² reviewed more than 20 studies. Subglottic pressure ranged from 0.275 to 25 kPa and airflow from 4 to 480 mL/s. In his own experiment, efficiency ranged from 10^{-2} to 10^{-7} . In the present study, similar results were obtained (see Table).

The advantages of this method are that it is

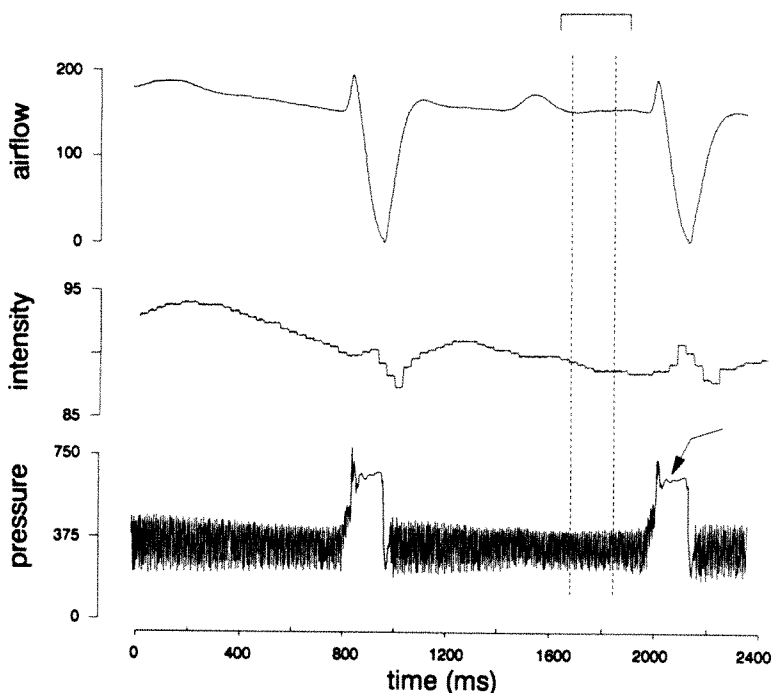


Fig 5. Representative sample of simultaneously acquired oral cavity pressure (pascals), airflow (milliliters per second), and sound intensity (decibels). Airflow, intensity, and frequency were measured during segment prior to occlusion of balloon (brackets). Subglottic pressure was measured at beginning of plateau (arrow).

RANGES AND MEAN VALUES OF SUBGLOTTIC PRESSURE, AIRFLOW, SOUND INTENSITY, AND LARYNGEAL EFFICIENCY

	Subglottic Pressure (Pa)	Airflow (mL/s)	Sound Intensity (W)	Laryngeal Efficiency (%)
Average	640	150	1×10^{-5}	9×10^{-5}
Minimum	309	14	5×10^{-10}	4×10^{-9}
Maximum	1,007	580	3×10^{-4}	3×10^{-3}

noninvasive and it does not interfere with the normal vibratory characteristics of the larynx. In addition, minimal special equipment is needed that is not otherwise available in a well-supplied voice or pulmonary functions laboratory. An initial time expenditure is necessary to set up the system, but once this is done, data are quickly and relatively inexpensively acquired.

The disadvantage of this technique is that it requires a significant amount of subject compliance and cooperation. In order for the premise of the airway interruption method to be supported, the subject must not alter phonation during the closure period. However, the natural tendency was for the subjects to push against the balloon. It was necessary

to instruct them to avoid this. To minimize the awareness of the closure period, it was made as brief as possible. This was done by adjusting the closure period until it was long enough to allow translaryngeal pressure to equilibrate but short enough so that the subjects would not react to the closure. Preliminary trials showed that 150 milliseconds was the optimal time.

One factor that affected the optimal duration of the closure period was the capacitance of the supraglottic airway. Theoretically, if the capacitance is high (eg, flaccid cheeks or pharynx) the air will continue to flow past the larynx during the closure period until the capacitance is reached. This means that the system will not be in a steady state and the oral cavity pressure will not equal subglottic pressure. In some subjects, presumably because of higher capacitance, the closure period was increased to 200 milliseconds to allow enough time for the pressures to equilibrate. To help decrease the capacitance of their upper aerodigestive tracts, these subjects were instructed to maintain a pursed embouchure on the mouthpiece. With these directions, almost all of the pressures could then be measured within 150 milliseconds.

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LIDOCAINE EFFECTS ON THE LARYNGEAL CHEMOREFLEX, MECHANOREFLEX, AND AFFERENT ELECTRICAL STIMULATION REFLEX

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The use of lidocaine hydrochloride as either a topical or intravenous agent has become a common practice for minimizing laryngospasm and the reflex cardiovascular effects resulting from upper airway manipulation. The efficacy and mechanism of action of lidocaine for this purpose remain unclear. We evaluated the effect of lidocaine on the laryngeal chemoreflex (LCR), mechanoreflex (LMR), and superior laryngeal nerve electrical stimulation adductor reflex (SLN-ESAR) in piglets. Cardiopulmonary responses were used to assess LCR and LMR. Latency following SLN stimulation was used to assess SLN-ESAR. Intravenous lidocaine hydrochloride at 3 mg/kg produced no suppression of the LCR, LMR, or latency (SLN-ESAR onset latency before lidocaine 11.7 ± 0.7 milliseconds, after lidocaine 12.2 ± 0.5 milliseconds; peak latency before lidocaine 13.2 ± 0.2 milliseconds, after lidocaine 13.4 ± 0.4 milliseconds). Topically applied lidocaine at the same dose eliminated both LCR and LMR responses in all animals, with return of reflex responses 15 minutes after application. No effect on the SLN-ESAR was seen with application of topical lidocaine. This study supports topical lidocaine as a suppressant of laryngeal mucosal neuroreceptors without central neural reflex effects. Intravenous lidocaine did not affect peripheral neuroreceptors, nor did it significantly affect the latency of the SLN-ESAR neural reflex arc. Intravenous and topical lidocaine differ in mechanism of action and efficacy with regard to modulation of reflex effects induced by laryngeal stimulation.

KEY WORDS — laryngeal adductor reflex, laryngeal chemoreflex, laryngeal mechanoreceptor, larynx, lidocaine, piglet.

INTRODUCTION

The reflexive physiologic effects of transglottic tracheal intubation include hypertension, tachycardia or bradycardia, elevation of intracranial pressure, cough, and laryngospasm.¹⁻³ Although laryngeal instrumentation is usually well tolerated, laryngeal reflexes can occasionally result in significant morbidity or mortality. Over the years attempts to modify the reflex responses to laryngeal manipulation have been made, with the mainstay of interventional techniques being the combination of sedative-hypnotic drugs plus intravenous or laryngeal topical lidocaine hydrochloride. Gilbert et al⁴ first reported the use of intravenous lidocaine hydrochloride as an adjunct to general inhalation agents in 1951. During the past four decades many articles have been published that either support or dispute the efficacy of lidocaine use during intubation, extubation, or laryngeal manipulation.^{1,2,5-12}

The laryngeal and tracheal mucosa is innervated by the sensory branches of the vagus nerve, and the physiologic effects of intubation are mediated primarily through afferent vagal reflexes.^{13,14} Several types

of laryngeal sensory receptors have been identified, including chemoreceptors, mechanoreceptors, chemo-mechanoreceptors, and cold receptors.¹⁵⁻¹⁷ These various receptors appear to be located within the mucosa and submucosa, and possibly in deeper laryngeal structures.

While stimulation of mechanoreceptors inevitably occurs with laryngeal manipulation, the reflex effects of chemoreceptor stimulation can be similar, and at times as severe.^{13,18} Previous work has shown that topical lidocaine blocks stimulus-induced superior laryngeal nerve (SLN) afferent fiber firing and also eliminates the physiologic side effects of stimulation of laryngeal chemoreceptors and mechanoreceptors.^{13,16,17} A large body of clinical work has shown that intravenous lidocaine can alter the physiologic reflex effects of glottic stimulation.^{2,3,5-7,9-12} However, the efficacy of intravenous lidocaine's modulation of laryngospasm clinically remains in question.⁸ Studies of intravenous lidocaine's effects on the more basic laryngeal reflex events in animal models in general are missing, and understanding of intravenous lidocaine's efficacy and site of action is lacking.

From the Departments of Otolaryngology-Head and Neck Surgery (McCulloch, Flint, Richardson), Anesthesiology (Bishop), and Medicine (Bishop), University of Washington, Seattle, Washington. Supported by the Department of Otolaryngology-Head and Neck Surgery Resident Research Fund. Dr McCulloch is currently in the Department of Otolaryngology-Head and Neck Surgery, The University of Iowa, Iowa City, Iowa. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Washington.

Presented at the meeting of the American Laryngological Association, Waikoloa, Hawaii, May 4-5, 1991. Winner of the Resident Research Award.

Cocaine has been shown to produce central respiratory depression when delivered to regions of the pontine medullary centers of the brain stem.¹⁹ Also, electroencephalographic changes consistent with cortical depression have been identified after intravenous lidocaine was used to supplement halothane inhalation anesthesia.²⁰ A similar central suppression of cough and laryngospasm has been proposed for intravenous lidocaine.^{21,22} However, no study has delineated this "central suppressive" effect of intravenous lidocaine on laryngopulmonary reflex events. Evaluating the effects of lidocaine on well-described and controlled laryngeal reflex phenomena such as the laryngeal chemoreflex (LCR) and the laryngeal adductor reflex could provide insight into the efficacy of lidocaine use during laryngeal manipulation in humans.

In a piglet model we evaluated the effects of topical and intravenous lidocaine on three well-described laryngeal reflexes: the LCR, the laryngeal mechanoreceptor reflex (LMR), and the superior laryngeal nerve electrical stimulation adductor reflex (SLN-ESAR) or laryngeal adductor reflex.

MATERIALS AND METHODS

Nine piglets 2 to 4 weeks old were studied. In five of the animals we studied the effects of lidocaine on the LCR and LMR. Four piglets were used to evaluate lidocaine effects on the SLN-ESAR.

The LCR and LMR are reflex responses to stimulation of the supraglottic laryngeal mucosa with either water (LCR) or pressure (LMR) and manifest as central apnea, cardiovascular changes, and reflex laryngeal closure. The SLN-ESAR is a reflex event initiated by electrical stimulation of the SLN and ending with glottic closure.

The animals were anesthetized with intramuscular ketamine hydrochloride (35 mg/kg) and xylazine hydrochloride (5 mg/kg), which was followed by one third of a dose of ketamine intravenously every 30 to 45 minutes if the animal showed signs of awakening. Each animal was placed supine over a heating pad set at 37°C. Femoral intravenous and arterial catheters were placed surgically. The arterial line was used to monitor blood pressure via a pressure transducer and for blood sampling. The venous line was used to administer fluids and deliver ketamine. A tracheotomy was performed and an endotracheal tube placed to maintain an airway. An anterior midline thyrotomy was performed and stay sutures were placed in the anterior commissure bilaterally. An 18-gauge needle was passed into the endotracheal tube, and endotracheal pressure changes were recorded and the waveform peaks counted to obtain respiratory rate. Trans-

cutaneous rhythm strip electrodes were placed and a cardiac rhythm was recorded. All data were recorded simultaneously on a Grass multichannel strip chart recorder.

Data from the strip chart recording included prestimulus and poststimulus pulsatile blood pressure, heart rate (HR) as counted from the cardiac rhythm strip recording, respiratory rates, and apnea length as counted from the respiratory pressure recording. The apnea length was considered to begin at the time of the final breath prior to water or mechanical stimulus and to end with the onset of regular respiration (more than one respiration within a 10-second period). Cardiovascular effects were assessed by evaluation of HR and mean arterial pressure (MAP). The MAP was calculated by the formula $MAP = [systolic\ BP + (2 \times diastolic\ BP)]/3$. The prestimulus levels were taken from the 30-second period just prior to laryngeal stimulation. The poststimulus blood pressure was recorded at the point of greatest hypotension during the apneic period or within 30 seconds poststimulus when no apnea or brief apnea occurred. Poststimulus HR was counted from the point of greatest bradycardia during the apneic period or within 30 seconds poststimulus when no apnea or brief apnea occurred.

The LCR was induced by placing 2 to 3 mL of water on the exposed supraglottic laryngeal mucosa. The mechanoreceptors were stimulated by placing an oversized endotracheal tube transorally and applying pressure to the supraglottis. Apneic response of greater than 3 seconds or hypopnea (respiratory depression of greater than 20% for 30 seconds or longer) with associated cardiovascular changes (a decrease in HR and MAP of more than 5%) was considered a positive response.

The SLN-ESAR was obtained by monopolar needle electrode recording. An intramuscular monopolar electrode was placed under direct visualization into the thyroarytenoid muscle, and a reference electrode was placed subcutaneously. The animal, nerve stimulator, and oscilloscope were grounded. The SLN was isolated and then directly stimulated with a monopolar nerve stimulator set at 1 to 2 V. The stimulus artifact and reflex compound motor unit action potential were recorded with a storage oscilloscope (Tektronix 2232 100-MHz digital storage oscilloscope) and later plotted and measured with a MacIntosh computer. Onset and peak latencies were measured.

The experimental design is outlined in Figs 1 and 2. Lidocaine levels were assessed by Roche Biomedical Laboratories (Sacramento, Calif). Differences in apnea and latency duration were assessed by using Student's *t* test for paired observations.

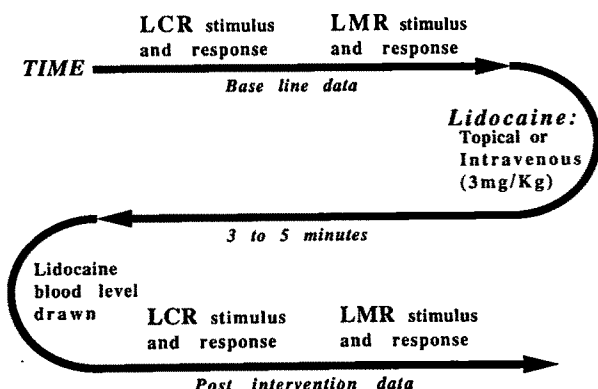


Fig 1. Experiment outline for laryngeal chemoreflex (LCR) and laryngeal mechanoreflex (LMR).

RESULTS

Laryngeal Chemoreflex and Mechanoreflex. Eight trials were run on five animals in the first study group. A reflex response with apnea occurred with stimulation of chemoreceptors and mechanoreceptors in all trials, both before and after administration of intravenous lidocaine. The mean duration of the apnea was shorter after lidocaine, but this difference was not statistically significant (Table 1). In both the prelidocaine and postlidocaine states, stimulation of the chemoreceptors induced a longer apnea duration compared to mechanoreceptor stimulation. An example of the LCR and LMR apnea data is shown in Fig 3. The group results of intravenous lidocaine effects on the LCR and LMR are shown in Table 1. The data are depicted as number and percent of positive reflex responses and mean apnea duration.

The cardiovascular effects of stimulation of the laryngeal chemoreflex and mechanoreflex were quite variable. A change in MAP and HR was identified in only 9 of 22 chemoreflex-induced apneas and during only 2 of 10 nonapneic trials (ie, after topical lidocaine). The cardiovascular effects of the mechanoreceptor stimulation were even less apparent. The cardiovascular changes associated with the chemoreflex apneas were not significantly different before versus after intravenous lidocaine: percentage of delta MAP before, -9.6 ± 15.0 , after, -2.4 ± 3.4 ($p = .26$); percentage of delta HR before, -4.9 ± 4.5 , after, -5.5 ± 3.7 ($p = .72$). The measured lidocaine levels 3 to 5 minutes after intravenous injection (3 mg/kg) had a value of $4.5 \pm 1.4 \mu\text{g/mL}$ (mean $\pm$ SE).

Topical lidocaine effects, again depicted as number and percent of positive reflex responses and mean apnea duration, are shown in Table 2. Topical lidocaine eliminated the LCR and LMR. The single positive response recorded in each group consisted of only a brief period of apnea without cardiovascular changes. All reflex responses had returned by 15 minutes after lidocaine administration.

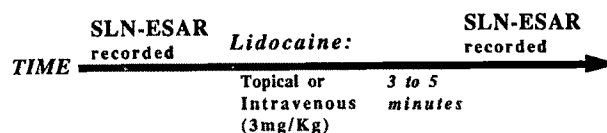


Fig 2. Experiment outline for superior laryngeal nerve electrical stimulation adductor reflex (SLN-ESAR).

Again, the small and variable cardiovascular responses of the chemoreflex were not significantly different before versus after topical lidocaine: percentage of delta MAP before, -2.9 ± 3.3 , after -6.7 ± 5.0 ($p = .29$); percentage of delta HR before, -4.8 ± 2.3 , after, 1.8 ± 4.5 ($p = .13$). Topical lidocaine did not produce a rise in blood lidocaine levels at 3 to 5 minutes postadministration.

Superior Laryngeal Nerve Electrical Stimulation Adductor Reflex. The waveforms presented in Fig 4 exemplify the SLN-ESAR recordings before and after intravenous lidocaine (3 mg/kg). Two waves were stored before and after lidocaine in each animal. The latencies were measured as onset latency and peak latencies.²³ The combined latencies from three animals are presented as mean and standard deviation in Table 3 (see also Fig 4). There is a trend toward a slight latency prolongation at all points of the SLN-ESAR after intravenous lidocaine in these animals, but latency differences did not reach significance. In one additional animal the 3-mg/kg dose of lidocaine was followed by a dose of 9 mg/kg, and again no change in SLN-ESAR was identified; onset latency at point "a" prelidocaine was 15.0 milliseconds, after 3 mg/kg was 15.1 milliseconds, and after 9 mg/kg was 15.0 milliseconds.

Topical lidocaine effects on the SLN-ESAR were recorded in only one animal. The onset latency at point "a" prelidocaine was 11.4 milliseconds, and postlidocaine was 11.8 milliseconds. The peak latency at point "b" prelidocaine was 13.2 milliseconds, and postlidocaine was 12.8 milliseconds.

DISCUSSION

Gilbert et al⁴ were the first to report use of intravenous lidocaine as an adjunct to general anesthesia. In

TABLE 1. EFFECTS OF INTRAVENOUS LIDOCAINE ON LCR AND LMR

	Before Lidocaine	After Lidocaine	p
LCR			
Positive response	100% (8/8)	100% (8/8)	
Apnea duration (s)	26 $\pm$ 17	18 $\pm$ 7	.13
LMR			
Positive response	100% (6/6)	100% (6/6)	
Apnea duration (s)	11 $\pm$ 8	8 $\pm$ 7	.18
LCR — laryngeal chemoreflex, LMR — laryngeal mechanoreflex.			

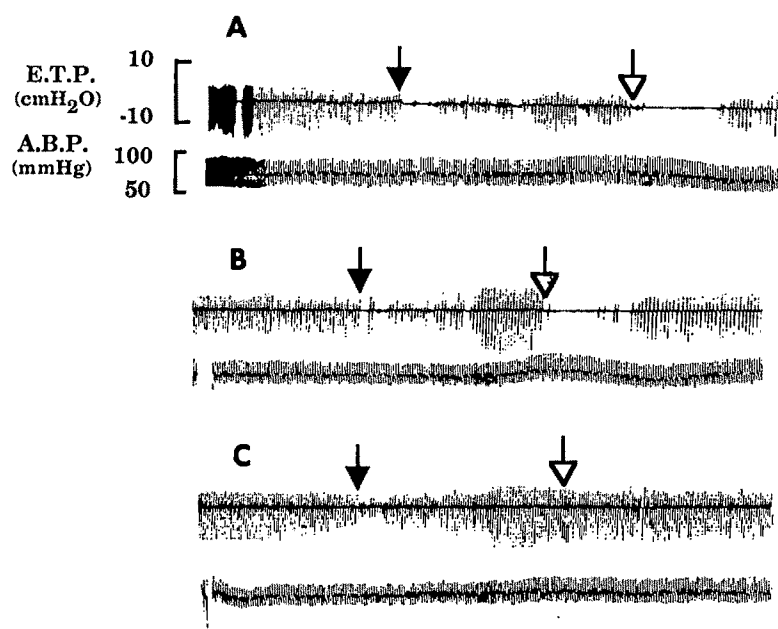


Fig 3. Effects of intravenous and topical lidocaine hydrochloride on laryngeal chemoreflex and laryngeal mechanoreflex. E.T.P. — endotracheal pressure (respiratory rate), A.B.P. — arterial blood pressure, closed arrow — point of mechanical stimulation, open arrow — point of chemical stimulation (H₂O). A) Before lidocaine. B) After intravenous lidocaine. C) After topical lidocaine.

the 1940s and 1950s there were reports of using the local anesthetic agents procaine and lidocaine intravenously to control pain and as adjuncts to general anesthesia.^{4,22,24,25} In 1951 Keats et al,²⁵ in a controlled study with procaine, concluded that these agents outside the operating room were only mildly effective for pain control and had major side effects.

In 1958, Steinhaus and Howland,²² reported that the addition of intravenous lidocaine to nitrous oxide-thiobarbiturate anesthesia suppressed pharyngeal and laryngeal reflexes without significant respiratory depression. Phillips et al²⁶ in 1960 evaluated intravenous lidocaine as an adjunct to thiopental, nitrous oxide, and succinylcholine in a blinded study and found that with the addition of lidocaine the dose of succinylcholine required was reduced by 17%, and the dose of thiopental used was reduced by 13%. Using rats in 1976, DiFazio et al²⁷ found that the cyclopropane concentration required could be reduced by 40% when intravenous lidocaine was added. The decreasing cyclopropane concentration was linearly related to lidocaine blood levels up to 1 µg/mL. Above this level a ceiling effect was reached. A year later Himes et al²⁸ looked at the effects of lidocaine

on the anesthetic requirements for nitrous oxide and halothane in humans. In that study anesthetic requirements could be reduced by 10% to 28% with lidocaine blood levels of 3 to 6 µg/mL, with a ceiling effect at approximately 5 µg/mL.

The interaction of lidocaine with the other agents may have synergistic effects on laryngeal reflex response. In our study animals were given ketamine. Ketamine is not a respiratory depressant and does not affect laryngeal reflexes alone.²⁹ Xylazine used as a single dose up front acts as a brief analgesic and muscle relaxant and is commonly used in animal studies.¹⁸ The addition of intravenous lidocaine to a barbiturate-containing anesthetic regimen may potentiate the suppression of laryngeal reflexes even with relatively low barbiturate doses. Lidocaine has been shown to act as a synergistic agent in maintaining deeper levels of anesthesia, and recent studies have shown that deeper levels of anesthesia affect laryngeal reflex events.^{30,31} It becomes difficult to sort out the anesthesia effects of lidocaine from its possible reflex suppressive effects. Although the cardiac and local anesthetic effects of lidocaine have been well described, the site and mechanism of action of lido-

TABLE 2. EFFECTS OF TOPICAL LIDOCAINE ON LCR AND LMR

TABLE 2. EFFECTS OF TOPICAL LIDOCAINE ON LCR AND LMR				
	Before Lidocaine	After Lidocaine		
		5 min	10 min	15 min
LCR				
Positive response	100% (8/8)	12% (1/8)	88% (7/8)	100% (8/8)
Apnea duration (s)	19 ± 8	0 ± 1	9 ± 5	11 ± 2
LMR				
Positive response	100% (6/6)	16% (1/6)	33% (2/6)	100% (4/4)
Apnea duration (s)	11 ± 8	0 ± 1	1 ± 1	8 ± 4
LCR — laryngeal chemoreflex, LMR — laryngeal mechanoreflex.				

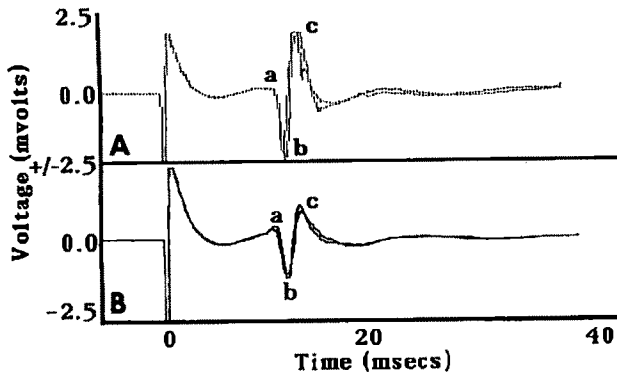


Fig 4. Effects of intravenous lidocaine hydrochloride on superior laryngeal nerve electrical stimulation adductor reflex. Values for points a, b, and c are given in Table 3. A) Before lidocaine. B) After intravenous lidocaine (3 mg/kg).

caine as a suppressant of laryngeal reflexes remain obscure. Topical lidocaine has been demonstrated to block or halt the chemolaryngeal reflex responses in animal studies. This effect is immediate and appears to be a primary mucosal neuroreceptor event.^{8,13,16} Intravenous lidocaine, however, may act at peripheral neuroreceptors, at specific central laryngeal reflex pathways, or nonspecifically by potentiating the general anesthetic effects of other agents.^{21,22,26-28}

As in previous studies, we found topical lidocaine to be a strong suppressant of tactile and chemolaryngeal reflexes, with a similar time frame of reflex return.^{32,33} The effect was immediate in onset, was of short duration, and occurred without an elevation in the lidocaine blood level. This finding implies a peripheral mucosal rather than a systemic or central effect for topical lidocaine. With intravenous lidocaine doses of 3 mg/kg and blood levels well into the therapeutic range of 1.5 to 5 mg/kg, we found no significant effect on the LCR or LMR. A decreased mean apnea duration after intravenous lidocaine was noted, but this was not statistically significant.

The recorded SLN-ESAR waveforms exemplified in Fig 4 are consistent in both latency and configuration with those produced in humans and in other animals.³⁴⁻³⁶ In this study the SLN-ESAR reflex arc remained intact and showed only a trend toward increasing latency after intravenous lidocaine at usual clinical doses. This latency increase was not significant in our group of animals. It is possible that with an increase in the number of animals studied the trends toward latency prolongation would reach statistical significance. Clearly, future study is warranted to address this issue. In addition, the effects of increasing the lidocaine dose have not been adequately studied; however, in order to obtain conduction delays in peripheral nerves by using intravenous lidocaine, toxic doses are required.³⁷ The clinical

TABLE 3. EFFECTS OF INTRAVENOUS LIDOCAINE ON SLN-ESAR

	Before Lidocaine	After Lidocaine	p
Latency a (ms)	11.7 ± 0.7	12.2 ± 0.5	.08
Latency b (ms)	13.2 ± 0.2	13.4 ± 0.4	.44
Latency c (ms)	14.8 ± 0.4	15.1 ± 0.3	.08

SLN-ESAR — superior laryngeal nerve electrical stimulation adductor reflex. Points a, b, and c are shown on Fig 4.

relevance of such studies would be limited by the lidocaine therapeutic window, since central nervous system side effects occur as plasma levels reach 5 µg/mL.³⁸

Intravenous lidocaine has been shown to be a strong suppressant of induced cough in awake patients, and cough suppression by intravenous lidocaine at the time of intubation has also been identified.^{6,7,10,11} Complete cough suppression was accomplished by doses of 2 mg/kg and with plasma levels greater than 3 µg/mL.⁷ Lidocaine may have a selective antitussive effect that we did not address.

Blancato et al²⁰ supplemented halothane inhalation anesthesia with intravenous lidocaine (4 to 5 mg/kg) during endoscopy and found a significant decrease in airway complications (laryngospasm, bronchospasm, and cyanosis) during the postoperative recovery period. These same patients were monitored with electroencephalography during the procedures, and postlidocaine waveform changes were identified that were consistent with cortical depression.²⁰ This and previous clinical studies support intravenous lidocaine as a central suppressant of some laryngopulmonary reflex events. However, our data do not support this conclusion.

Threshold changes were not evaluated in this study, and it is possible that changes in stimulus response thresholds occur with intravenous lidocaine. The reported ability of intravenous lidocaine to decrease the risk of laryngospasm and cough at times of laryngeal manipulation is possibly due to effects on response thresholds. The ability of intravenous lidocaine to deepen level of anesthesia most likely also plays a role in the clinically identified effects.

CONCLUSION

Intravenous and topical lidocaine appear to differ in mechanism of action and efficacy with regard to modulation of reflex effects induced by laryngeal stimulation in the piglet. Elimination of LCR and LMR produced by topical lidocaine and persistence of LCR and LMR following intravenous lidocaine imply that the principal site of action for topical lidocaine is at the peripheral receptors. The clinical literature supports a central lidocaine effect that could not be identified in this animal model. Only trends

toward latency prolongation in the SLN-ESAR and decreased LCR and LMR apnea durations after intravenous lidocaine hint at this presumed central effect of lidocaine. The clinically identified intravenous lidocaine effects may be secondary to lidocaine's effect on depth of anesthesia, as opposed to a specific

central effect on laryngeal reflex events. Future studies addressing the effects of lidocaine on stimulus thresholds and reflex latencies, and the combined effects of lidocaine and anesthetic agents may add further insight to the role of lidocaine as a suppressant of laryngeal reflex events.

ACKNOWLEDGMENTS — We thank Greg Damiano, Sandra M. Guidotti, and Marc D. Coltrera, MD, for technical assistance.

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The UCSF Otolaryngology Update: 1992, will be held November 5-7, 1992, at the Ritz-Carlton Hotel in San Francisco, California. For more information, contact the University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; telephone (415) 476-4251.



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MENIERE'S SYNDROME INHERITED AS AN AUTOSOMAL DOMINANT TRAIT

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Brown in 1941 reported on five families having two members with Meniere's syndrome. In 1949 she reported on three siblings (children of first cousins) and two identical twins bearing the syndrome. Bernstein in 1965 reported on seven families having two or more members afflicted by the symptoms. All these reports showed association between Meniere's syndrome and migraine headaches. None provided detailed pedigree studies in order to clarify the mode of genetic transmission. We report on a father, three daughters, and one son with typical Meniere's syndrome and paroxysmal headaches. The pedigree strongly suggests autosomal dominant transmission. After studying this family we have been paying close attention to family histories of Meniere's syndrome patients. It is not at all uncommon to hear about other members of the family with the syndrome, but it is difficult to document all of the cases for logistical reasons.

KEY WORDS — genetic transmission, headache, Meniere's syndrome.

Familial incidence of Meniere's syndrome was reported by Brown in 1941¹ and 1949² and by Bernstein³ in 1965. Although there were no detailed pedigree studies included in these reports, the three siblings, children of first cousins, described by Brown² suggest autosomal recessive transmission, while several kindreds described by Bernstein³ suggest autosomal dominant transmission. These reports led Konigsmark and Gorlin⁴ to believe that there are two kinds of hereditary deafness associated with vestibular symptoms: one recessively transmitted and the other dominantly transmitted. These should be differentiated from idiopathic sporadic Meniere's syndrome ("true" Meniere's disease).

Migrainelike headache attacks were strongly associated with Meniere's syndrome in several families described by Brown¹ and Bernstein,³ and this finding could lead one to associate migraine headache specifically with hereditary Meniere's syndrome. However, Dolowitz⁵ in 1979 studied 127 patients with sporadic Meniere's syndrome and found 27 signs and symptoms present often enough to be considered relevant. Nine symptoms showed a high frequency of occurrence, among them the classic Meniere's triad and paroxysmal headache. Further statistical analysis showed that headache was an independent symptom (not associated with the other core symptoms except tinnitus).

The following questions come to mind when studying hereditary Meniere's syndrome. 1) Is it a separate and rare syndrome that must be differentiated from its sporadic counterpart, or is it the same syndrome in which a genetic component is more evident? 2) How does one explain the strong association of Meniere's

syndrome, both hereditary and sporadic, with headache that is often present but seems to be independent of the other symptoms?

We report on a father, three daughters, and a son with typical Meniere's syndrome and headache whose pedigree study strongly suggests an autosomal dominant mode of transmission and attempt to shed some light on the two questions outlined above.

FAMILY DESCRIPTION

Figure 1 shows the pedigree study of the proband's first family. Meniere's syndrome appeared for the first time in the father (proband) of four daughters and three sons, of whom three of the daughters and one of the sons have the syndrome as documented by us. One son and one daughter are known to have the symptoms, but were not available for further documentation. The mother died when she was 36 years old and had never had vertigo, tinnitus, or noticeable hearing loss. She never had had an audiogram. None of her five brothers have the syndrome and there were no affected siblings in the previous generation of her family. There was no consanguinity between the proband and his first wife. The inset in Fig 1 shows the available genetic information on the proband's second family. There are three daughters and three sons. One daughter is known to have the syndrome, but was not available for further documentation. The second wife is alive and is symptom-free, as are her two brothers and two sisters.

We present in the following paragraphs the case histories and audiometric, electronystagmographic, and laboratory findings on the five cases we have

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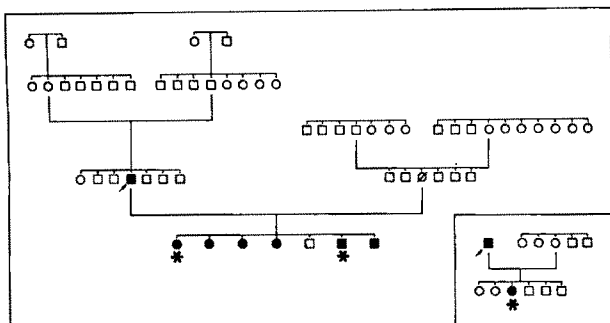


Fig 1. Schematic representation of pedigree of described family. Light circle — unaffected female, light square — unaffected male, dark circle — affected female, dark square — affected male, arrow — proband, crossed circle — deceased female, asterisk — sibling known to have syndrome by history but unavailable for documentation. Inset) Proband's second family.

The information used to reconstruct the family trees was obtained by the senior author (C.A.O.), who carefully interviewed the father and each of the affected members of the family who were examined and whose cases are documented below.

CASE REPORTS

Patient 1. The father of the four affected siblings was 69 years old at the time of examination. He was seen for the first time at the Otolaryngology Clinic of the University Hospital, Brasília University Medical School, in April 1980, complaining of severe episodic rotatory vertigo with drop (falling) attacks, tinnitus, and fluctuating hearing loss in the right ear of 5 years' duration. The drop attacks were severe and he had hurt himself several times. Right-sided headache usually preceded the crisis. An audiogram (Fig 2A) showed a flat sensorineural hearing loss in the right ear and a down-sloping curve on the left side. Polytomograms of the internal auditory canals were normal. Results of routine blood tests and physical examination were normal. A diagnosis of Meniere's disease in the right ear was made, and a right endolymphatic sac drainage procedure was performed in May 1980. The patient was interviewed and his hearing was tested again in June 1990. His vertigo has been markedly improved and he has had no drop attacks since the operation; however, he still has vertiginous attacks, controlled by medication, and hearing in the left ear has markedly deteriorated (Fig 2B). Tinnitus is still present bilaterally and his headache is unchanged. He is happy with the result of the operation because it resolved his worst symptom: the drop attacks. A VDRL test was negative and a glycerol test was positive bilaterally.

1990 complaining of paroxysmal rotatory vertigo described as intense, fluctuating hearing loss, and tinnitus that was bilateral but worse in the right ear. She has intense headaches preceding the vertiginous attacks and often related to her menstrual periods. These symptoms had started 10 years before. Findings on physical examination were normal, as were results of VDRL, blood cholesterol, and triglyceride testing. An audiogram (Fig 2C) showed a moderate bilateral sensorineural hearing loss with an up-sloping curve, worse in the right ear; and a glycerol test was positive bilaterally. Routine mastoid radiographs were normal. A diagnosis of bilateral Meniere's disease was made, and an endolymphatic sac drainage procedure was offered for the right ear, but the patient has not made up her mind about the operation as yet. Presently her vertigo is precariously controlled by medication.

Patient 3. The 40-year-old sister of patient 2 was seen by us in September 1990. She complained of severe episodic rotatory vertigo, fluctuating hearing loss, and tinnitus that was bilateral but worse in the left ear. The symptoms had started 3 years before. Findings on physical examination and VDRL, blood cholesterol, and triglyceride testing were normal, as were routine mastoid radiographs. An audiogram (Fig 2D) showed a moderate sensorineural hearing loss with up-sloping curves that was bilateral but worse in the left ear. A glycerol test was positive bilaterally. An electronystagmogram was normal on both sides. The patient denied headaches. Presently her vertigo is controlled by medication.

Patient 4. The 21-year-old daughter of the family was seen by us in September 1990, complaining of episodic rotatory vertigo and bilateral tinnitus. She denied subjective hearing loss. Headache accompanied the vertiginous attacks and was of moderate intensity. Findings on physical examination, routine mastoid radiographs, and blood cholesterol, triglyceride, and VDRL testing were normal. An audiogram (Fig 2E) shows a slight sensorineural hearing loss with an up-sloping curve on both sides but worse in the right ear. A glycerol test was positive bilaterally and an electronystagmogram was normal. The patient's vertigo is presently controlled by medication.

Patient 5. The 38-year-old brother of the female patients was seen by us in September 1990. He complained of episodic vertiginous attacks, tinnitus, and fluctuating bilateral hearing loss. The symptoms had started 2 years before, and headache usually preceded a crisis. Findings on physical examination and routine mastoid radiographs were normal. An

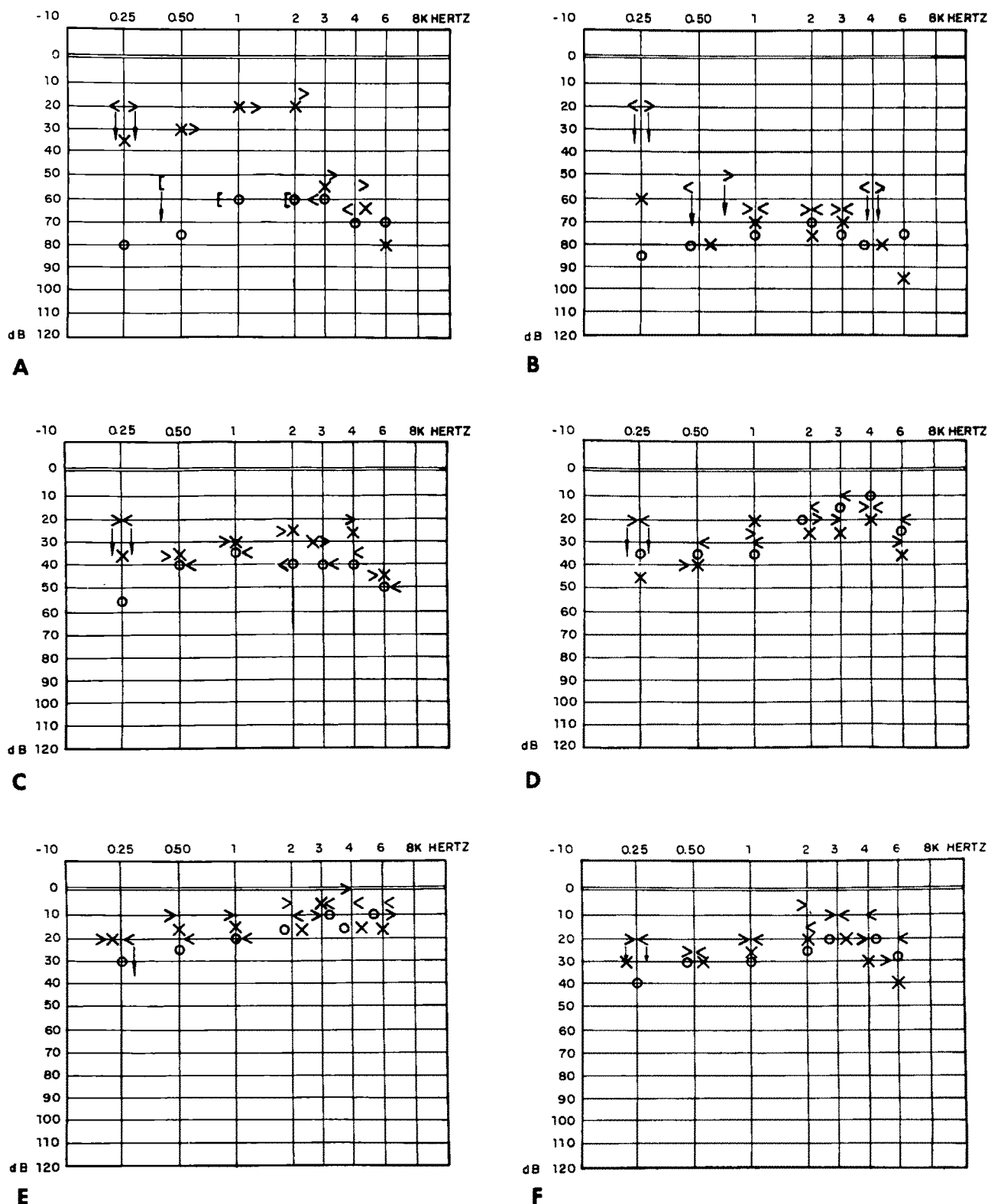


Fig 2. Audiograms. A,B) (Patient 1) A) April 1980 (before endolymphatic sac drainage in right ear). Audiometric curve of right ear is compatible with advanced Meniere's disease, while that of left shows only presbycusis. B) June 1990. Hearing in right ear has not changed substantially, but that in left ear has deteriorated markedly, and audiometric curve is now compatible with advanced Meniere's disease. C) (Patient 2) June 1990. Bilateral moderate sensorineural hearing loss with up-sloping configuration, worse in right ear. D) (Patient 3) September 1990. Bilateral moderate sensorineural hearing loss with up-sloping configuration, worse in left ear. E) (Patient 4) September 1990. Bilateral slight sensorineural hearing loss with up-sloping configuration, worse in right ear. F) (Patient 5) September 1990. Bilateral slight sensorineural hearing loss with up-sloping configuration, worse in right ear.

audiogram (Fig 2F) showed a slight bilateral sensorineural hearing loss with an up-sloping curve, worse in the right ear. A glycerol test was positive in both ears. The patient's vertigo is presently controlled by medication.

COMMENTS

In all five patients, we were able to document typical Meniere's syndrome (paroxysmal rotatory vertigo, tinnitus, and fluctuating hearing loss). All but one (patient 3) had episodic headache, and all had both ears affected by the disease as documented by bilateral tinnitus, bilateral low-frequency sensorineural hearing loss, and a positive glycerol test in both ears. The high incidence of migrainelike headaches in patients with hereditary Meniere's syndrome has been pointed out before,¹⁻³ but the majority of patients reported by Brown^{1,2} and Bernstein³ had only one ear involved.

Pedigree study of the family we described (Fig 1) strongly suggests an autosomal dominant mode of genetic transmission. The presence of one affected female in the proband's second family supports this view. Previous reports¹⁻³ did not provide detailed pedigree studies, but most families described seemed to follow an autosomal dominant pattern. One family described by Brown² showed consanguinity between the parents, and on this basis only was supposed by Konigsmark and Gorlin⁴ to follow an autosomal recessive mode of transmission. The family we described supports the existence of an autosomal dominant mode of transmission for inherited Meniere's syndrome. The existence of an autosomal recessive one must await further evidence to be confirmed.

Genetically transmitted Meniere's syndrome has been said to be rare and different from sporadic Meniere's syndrome.⁴ The first patient we described suffered from severe vertiginous episodes with drop attacks and was much improved by an endolymphatic sac drainage procedure in his right ear. Ten years after this operation his vertiginous episodes are still under control, and hearing in the ear operated on is almost the same as in the left one, which was involved by the disease much later (Fig 2A). This outcome certainly suggests that the inherited Meniere's syndrome is really no different from the sporadic one ("true" Meniere's disease). Another feature that could be used to differentiate inherited from sporadic Meniere's syndrome is the presence of migrainelike attacks associated with the former. However, Dolowitz⁵ has shown that headache is indeed one of the

core symptoms in sporadic Meniere's syndrome as well.

After studying this family we have systematically asked patients with idiopathic Meniere's syndrome (Meniere's disease) about other members of the family affected by the symptoms. One patient we have been following up for many years said his father had the same symptoms up to the time of his death and that migrainelike headaches were common among his relatives. It has been our impression that when we ask them, it is not at all uncommon to hear from patients with Meniere's disease about other members of the family affected by the symptoms, although it is very difficult to document all the related cases for logistical reasons.

We feel it is conceivable that all patients with Meniere's disease have a genetic determinant that most of the time is sporadic but may occasionally be transmitted as an autosomal dominant trait.

There have been many theories about the cause of Meniere's disease. Some of them⁵⁻⁸ postulate a central nervous system cause: through the autonomic nervous system the microcirculation in the inner ear would be affected, leading to inner ear fluid imbalance and to the production of the symptoms. Endolymphatic hydrops would be a parallel phenomenon, not the cause of the symptoms, and migrainelike headaches would occur as a consequence of microvascular changes in the central nervous system. These theories fittingly explain the occurrence of headache as a core symptom in Meniere's disease but one that is dissociated from the other (inner ear) symptoms. The basic change in the central nervous system would be genetically determined as in migraine or epilepsy. Of course, these are only theories waiting for experimental proof. The fact that the symptoms of Meniere's disease may be present in patients without endolymphatic hydrops⁹ and that hydrops may be present without the symptoms of Meniere's disease¹⁰ seems to support this line of thought. Furthermore, it has recently been shown by the senior author that there is no correlation between endolymphatic hydrops and tinnitus in patients with Meniere's disease.¹¹

CONCLUSIONS

For now, the following statements appear safe.

1. There is an autosomal dominant mode of transmission for Meniere's syndrome.
2. Meniere's syndrome inherited as an autosomal dominant trait seems to be no different from its sporadic counterpart ("true" Meniere's disease).

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PEDIATRIC AIRWAY RECONSTRUCTION AT GREAT ORMOND STREET: A TEN-YEAR REVIEW

II. REVISIONAL AIRWAY RECONSTRUCTION

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One hundred eight consecutive patients with pediatric laryngotracheal stenosis requiring airway reconstruction over a 10-year period were reviewed. Thirty-two patients required revisional airway reconstruction in an attempt to achieve decannulation. Patients underwent from one to four revisional airway reconstructions, most often laryngotracheal reconstruction with costal cartilage grafting. In the Cotton grading scheme of preoperative stenosis, those patients requiring revisional airway surgery tended to come from the more severely affected categories. Twenty-two patients of 32 (69%) achieved decannulation with revisional airway reconstruction. Thus, revisional airway reconstruction is indicated if the first attempt fails.

KEY WORDS — cartilage, intubation, laryngotracheal stenosis, tracheostomy.

INTRODUCTION

After a patient undergoes primary airway reconstruction, follow-up microscopic laryngoscopy and bronchoscopy are done to assess the size of the airway lumen in preparation for decannulation. The majority of patients are able to be decannulated after one attempt at airway reconstruction. Some patients, however, suffer restenosis of the airway in spite of the augmentation procedure. These patients require another attempt at increasing the airway diameter so that decannulation can be accomplished.

This article is devoted to examining this particular patient population in the general management of pediatric laryngotracheal stenosis.

MATERIALS AND METHODS

A search was undertaken to identify all patients with pediatric laryngotracheal stenosis at The Hospital for Sick Children, Great Ormond Street, who required revisional airway reconstruction from January 1, 1978, to January 1, 1988. These medical records were reviewed in January 1990, so that all patients studied would have a minimum of 2 years of postoperative follow-up. A general review appears in an earlier article.¹

The degree of preoperative stenosis was assigned to one of four groups as described by Cotton et al.² Grade 1 obstruction had less than 70% of obstruction of the lumen; grade 2 had between 70% and 90% of

the lumen obstructed. Grade 3 cases exhibited greater than 90% obstruction, but still had an identifiable lumen. Grade 4 stenosis existed when no lumen or fistula was present and no vocal cords were recognized; hence, grade 4 is a pouch with no epidermal connection.

RESULTS

One hundred eight patients required airway reconstruction during the study period. Thirty-two (30%) patients required revisional airway reconstruction in an attempt to achieve decannulation. Revisional surgeries consisted of 8 laryngotracheoplasties³ and 40 laryngotracheal reconstructions with costal cartilage grafting.⁴ If a laryngotracheoplasty was done as the first revisional operation and further surgery was required, laryngotracheal reconstruction with costal cartilage grafting was done. The time elapsed from primary to revisional reconstruction was most often 13 months, but varied from 2 months to almost 4 years.

Those requiring revisional surgery tended to have worse stenoses upon presentation and tended to come from the higher-grade categories. Only 4% of grade 1 patients required revisional airway reconstruction, but 63% of grade 4 patients did (Fig 1). There was evidence of gastroesophageal reflux in only two patients, and this condition was specifically looked for in the medical records reviewed. Reflux investi-

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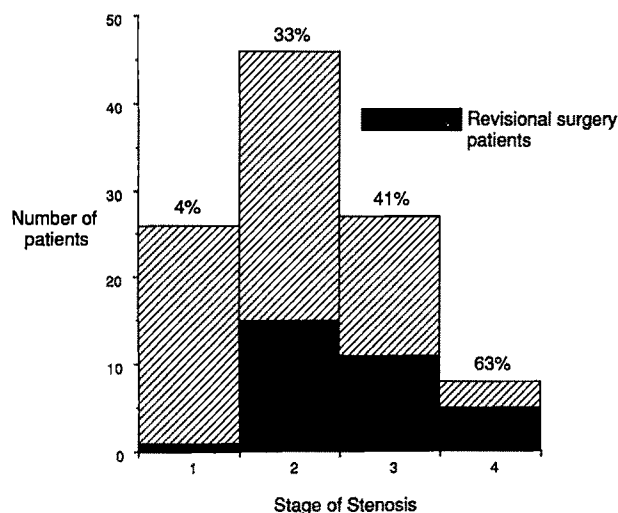


Fig 1. Patients requiring revisional airway reconstruction. Only 4% of grade 1 patients required revisional airway reconstruction, whereas 63% of grade 4 patients did.

gations were not routinely performed during the study period.

The number of revisional operations varied from one to four. Sixty-nine percent (22 of 32) of the revisional surgical patients were successfully decannulated (Fig 2). This compares with 89% (68 of 76) of patients decannulated after the first attempt at airway reconstruction.

DISCUSSION

Revisional airway reconstruction poses an even more challenging problem in the already difficult area of managing pediatric laryngotracheal stenosis. The anatomic landmarks are distorted by the previous surgery and resulting fibrosis.

Laryngotracheoplasty requires well-defined landmarks for the castellated incision, whereas laryngotracheal reconstruction depends on a midline incision. It is because of these increased technical difficulties in revisional airway reconstruction that laryngotracheal reconstruction with costal cartilage grafting is favored over laryngotracheoplasty.

Revisional airway reconstruction patients may be comparable to repeat cricoid split patients, who benefit from more than one attempt at extubation. The cricoid split is an operation designed to avoid a tracheostomy in intubated children with laryngotracheal stenosis. Patients who fail a primary cricoid split will often be able to be extubated after a repeat cri-

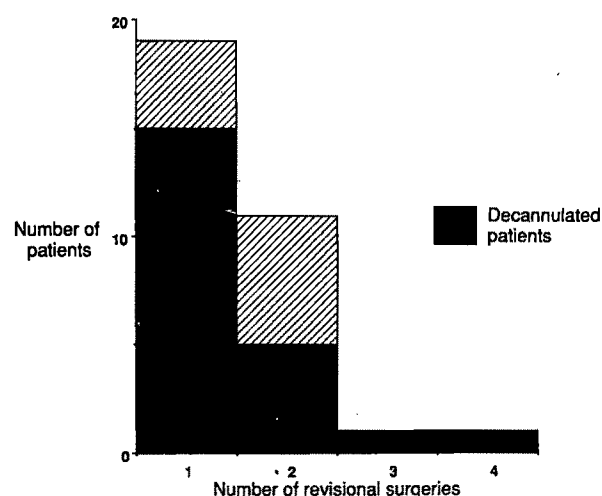


Fig 2. Decannulation rates after revisional airway reconstruction. Number of revisional operations varied from one to four. Sixty-nine percent (22 of 32) of revisional surgical patients were successfully decannulated.

coid split.⁵

Gastric acid has been shown in an animal model to induce subglottic fibrosis, and thus gastroesophageal reflux has been linked to failure of airway reconstructive surgery.^{6,7} Surprisingly, only 2 of the 32 revisional surgical patients had reflux symptoms that were severe enough to be observed clinically. Probably many more revisional surgical patients had asymptomatic or "silent" reflux, an issue that has received increasing attention recently (S. M. Pransky, unpublished data, 1991). These patients must be identified and treated so that surgery will have a greater chance of success. In the future, reflux investigations will be done to identify patients with silent reflux causing airway stenosis.

There is no clinical sign or test that helps to distinguish patients who will be able to be decannulated after one airway reconstruction from those who will need more than one procedure. The Cotton staging scheme of preoperative stenosis severity was helpful, however, in that those patients who are at increased risk of needing revisional surgery tend to come from the more severely affected groups.

Revisional surgery is effective, since about 69% of the patients who initially fail will be able to be decannulated after the surgery.

The last article in this three-part series will deal with the issues of decannulation and suprastomal collapse.

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THIRD INTERNATIONAL CONFERENCE ON PEDIATRIC OTORHINOLARYNGOLOGY

The Third International Conference on Pediatric Otorhinolaryngology of the "European Pediatric Otolaryngology Working Group" will be held in Jerusalem, November 7-12, 1993. For more information, contact Prof Jacob Sadé, 14 Hagefen St, Ramat-Hasharon 47254, Israel; telephone 972-3-5494275; fax 972-3-655674.



INTERNATIONAL HEARING AID CONFERENCE GENERAL ANNOUNCEMENT AND CALL FOR PAPERS

An International Hearing Aid Conference will be held June 15-17, 1993, at The University of Iowa, Iowa City. For information on registration and accommodation, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231, fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

ORBITAL COMPLICATIONS OF ACUTE SINUSITIS: COMPARISON OF COMPUTED TOMOGRAPHY SCAN AND SURGICAL FINDINGS

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The accuracy of computed tomography (CT) in distinguishing an abscess from cellulitis in children who present with orbital manifestations of paranasal sinus infection remains in question. In this 10-year retrospective study, CT results are compared with surgical findings in 19 patients with orbital complications who underwent surgical exploration within 24 hours of their CT scans. Fifteen of the 19 CT scan interpretations indicated abscesses that were verified intraoperatively. Two patients had negative surgical explorations despite CT interpretations predicting abscesses. An abscess was also surgically documented in 1 of 2 patients whose preoperative scans indicated cellulitis alone. We conclude that the correlation between radiologic and operative findings in 16 of these 19 cases, although not absolute, does substantiate the use of CT scanning as a therapeutic guide in children presenting with orbital disease secondary to paranasal sinusitis.

KEY WORDS — computed tomography, orbital abscess, orbital cellulitis, paranasal sinusitis.

Orbital complications of paranasal sinusitis have been recognized for at least 50 years.^{1,2} The most commonly used classification divides such complications into inflammatory edema (preseptal cellulitis), orbital (postseptal) cellulitis, subperiosteal abscess, orbital abscess, and cavernous sinus thrombosis.³ The literature demonstrates a variety of management approaches for children with such complications.^{4,5}

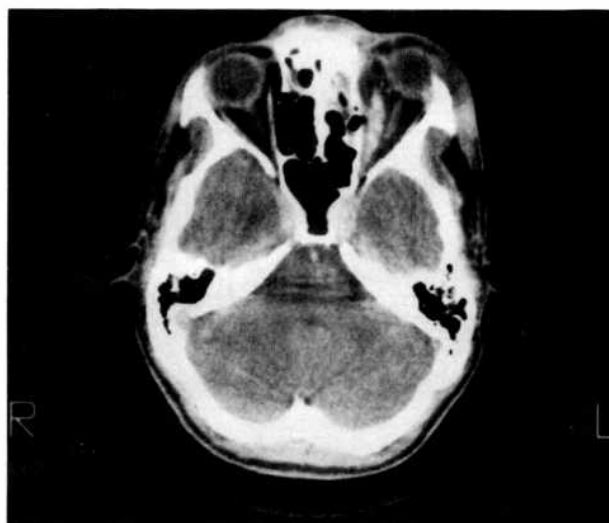
Progressive proptosis and chemosis with ophthalmoplegia and visual impairment are the clinical findings that typically prompt consideration of surgery. Ophthalmologic examination, particularly the assessment of visual acuity, can be difficult in children. Radiologic assessment of the orbit by means of plain radiographs, ultrasonography, and especially computed tomography (CT) is very much relied on in this age group.⁶ Although CT scanning has been increasingly accepted as the preferred radiologic modality for differentiating the orbital complications of paranasal sinusitis, there are reports in isolated cases of disparities in results between CT and surgical findings.⁷⁻⁹ Since an abscess within the confines of the bony orbit requires treatment by surgical exploration and drainage, distinguishing between cellulitis and abscess in children is critical.

The impetus for this study was an index child in whom a preoperative CT scan predicted a subperiosteal abscess that was not verified at the time of immediate surgical exploration (see Figure). Our working hypothesis was that CT findings could be mislead-

ing for critical decision-making in children with orbital sequelae of paranasal sinus infection.

METHODS

We reviewed the medical records of 78 pediatric patients less than 18 years of age who received diagnoses of orbital or periorbital infections at the Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital between 1980 and 1990. These records were examined to identify patients whose hospital course met the following criteria: 1) an or-



Axial image with contrast enhancement interpreted as left subperiosteal abscess. No abscess was found at surgical exploration.

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Presented at the meeting of the Society for Ear, Nose and Throat Advances in Children, Washington, DC, December 7-9, 1990.

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COMPARISON OF SURGICAL AND CT SCAN FINDINGS

Subject	CT Scan Report	Surgical Findings	Contrast (+/-)	Imaging Plane(s) (Axial/Coronal)	Adjacent Sinus
1	SPA	SPA	+	A/C	Ethmoid
2	SPA	SPA	+	A/C	Ethmoid
3	SPA	SPA	+	A/C	Frontal
4	OA	OA	+	A/C	Ethmoid
5	SPA	SPA	+	A/C	Ethmoid
6	SPA	SPA	+	A/C	Ethmoid
7	SPA	SPA	+	A/C	Ethmoid
8	SPA	SPA	+	A/C	Frontal
9	SPA	SPA	+	A/C	Ethmoid
10	OA	OA	-	A/C	Ethmoid
11	SPA	SPA	-	A/C	Frontal
12	SPA	SPA	+	A	Ethmoid
13	OA	OA	+	A	Frontal
14	SPA	SPA	+	A	Ethmoid
15	SPA	SPA	+	C	Frontal
16	SPA	Cellulitis	+	A/C	Ethmoid
17	SPA	Cellulitis	+	A	Ethmoid
18	Cellulitis	SPA	-	A/C	Ethmoid
19	Cellulitis	Cellulitis	+	A/C	Ethmoid

CT — computed tomography, SPA — subperiosteal abscess, OA — orbital abscess.

bital infection of paranasal sinus origin, 2) a formal written radiologic interpretation for a CT scan performed at these institutions, and 3) written documentation of surgical findings at orbital exploration done within 24 hours of the CT scan. The operative findings were compared with the CT scan interpretations.

RESULTS

Nineteen of the 78 patients satisfied the above criteria (see Table). Of these 19, 15 were children in whom the CT scan indicated an abscess and the surgical exploration verified the presence of purulent fluid. The CT scan in 2 other patients suggested abscess formation that was not identified during surgery. In the 2 remaining patients, the CT findings were interpreted as cellulitis with no evidence of abscess. Both patients were explored for failure to respond to medical therapy. In 1 child, an abscess was found; no abscess was identified in the other child. In summary, in 16 of the 19 children (84%) the operative findings correlated with the preoperative CT interpretations.

The patients were also categorized by orbital disease location relative to the periorbital and apparent sinus of origin (see Table). Sixteen of the 19 CT scans indicated subperiosteal involvement, including the 2 scans read as cellulitis. The remaining 3 scans revealed extraconal orbital abscesses. Fourteen CT scans showed the inflammatory process to be adjacent to the ethmoid sinuses; the other 5 scans indicated the abscess to be centered near the unilateral frontal sinus.

Additional information was obtained from the records in an attempt to identify the optimum scanning protocol. Primarily two types of CT scanners were used over the course of this study. Thirteen of the patients were imaged with a Siemens Somotron scanner; in 4 cases a GE 9800 scanner was used; the medical records did not identify the exact scanner used to assess the remaining 2 patients. Intravenous contrast media was used in 16 of the 19 cases. Both axial and coronal projections were used in 12 studies. Seven radiologists were involved in the interpretations.

DISCUSSION

Strict entrance criteria were used to enhance the validity of this retrospective study. Many of the original 78 children were transferred to our institutions with CT scans completed at the referring hospitals. By including only those children whose CT scans were performed at our institutions, we attempted to minimize differences in imaging technique and radiologic interpretation. The 24-hour time span between CT scan performance and surgical exploration was invoked so that progression or improvement of disease would not adversely influence the outcome of our comparisons.

This study was performed from a surgical perspective. Radiologic consultation for CT assessment was requested, with no attempt to control imaging parameters. The use of contrast enhancement and coronal as well as axial projections in CT imaging of children with orbital complications is not a uniform practice. Towbin et al¹⁰ reported accurate imaging of subperiosteal

teal and orbital abscesses without contrast enhancement using axial projections; others have argued that the use of both intravenous contrast and coronal projections markedly improves imaging accuracy.¹¹ It is noteworthy that our false-positive (subjects 16 and 17) and false-negative (subject 18) cases occurred both with and without the use of contrast enhancement and coronal views (see Table), so that no optimal scanning protocol could be retrospectively defined.

The vast majority of the cases were subperiosteal processes adjacent to the ethmoidal sinuses, reflecting the well-established common spread of infection through bony dehiscences in the lamina papyracea or along vascular and neural ethmoidal foramina. Retrograde hematogenous spread through valveless veins of the superior and inferior venous plexus and, less commonly, systemic hematogenous seeding are alternative routes of orbital infection. The radiologic documentation of abscesses in proximity to the frontal

sinuses in five children is particularly important in this regard. The CT scans in these five cases directed surgical management to include drainage of the frontal sinuses in addition to ethmoidectomy.

CONCLUSION

The evaluation of children with orbital complications from paranasal sinusitis can be challenging. Prompt decision-making may help preserve vision or prevent additional ophthalmologic complications. Our study further supports the use of CT scanning in the preoperative orbital assessment of such children, with the understanding that the radiologic documentation of the presence or absence of a subperiosteal or orbital abscess may be inexact. Surgical exploration, regardless of CT findings, is recommended in children who initially present with decreased visual acuity or who demonstrate progression of orbital manifestations despite medical therapy.

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PLANUM SEMILUNATUM OF THE RAT: NEW LIGHT AND ELECTRON MICROSCOPY OBSERVATIONS

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Planum semilunatum (PSL) cells of the rat ampullae were studied by light, transmission, and scanning electron microscopy. The observed ultrastructure of rat PSL cells was similar to that described in other species, but is in disagreement with earlier reports of rat PSL cells, most probably because of previous divergent definitions of the PSL. Regions of PSL cells were easily distinguished from other nonsensory epithelia at the lateral ends of the crista ampullaris. The PSL region consisted of irregular-shaped columnar to cuboidal pentagonal or hexagonal cells that interdigitated with one another by lateral membrane infoldings. In the PSL region the subepithelial reticular layer appeared thickened and formed wartlike impressions in the basal surface of the PSL cells. These morphological characteristics of the subepithelial reticular layer were unique to the PSL region in the ampulla and may reflect special adaptations of the PSL region to mechanical stress. Furthermore, the thick subepithelial reticular layer may have implications for transport across the PSL region.

KEY WORDS — ampulla, inner ear, morphology, nonsensory epithelium.

INTRODUCTION

Definition of the planum semilunatum (PSL) over the years has been rather broad. The PSL was originally described by Steifensand¹ in 1835 as the "halbmondförmige Fläche der Ampullenhaut, wo der verschmälerte Rand des Septum sich an die Seitenwände ansetzt" ("half-moon-shaped area of the ampullar skin in which the narrow side end of the crista ampullaris inserts into the ampullar side wall"). Nonetheless, several authors considered all specialized secretory cells surrounding the crista ampullaris as constituting the PSL.²⁻⁵ Later, Dohleman^{6,7} and Kimura et al⁸ emphasized the distinct morphological differences among nonsensory epithelial cells of an ampulla. Hence, the specialized epithelium at the lateral ends of the crista ampullaris was designated as the PSL (Fig 1). The ultrastructure of the PSL cells, however, remains an area of confusion in recent literature. The PSL cells have been described as being similar morphologically to dark cells and also to transitional cells.⁹

The PSL has been studied in several species, eg, pigeon,⁷ guinea pig,⁸ squirrel monkey,¹⁰ and rat.¹¹⁻¹³ The PSL cells were uniformly described as partly columnar or cuboidal, with their lateral membranes interdigitating with adjacent cells. Aberrantly, the ultrastructure of rat PSL cells was described as containing many infoldings on the basolateral membranes.¹¹⁻¹³ Furthermore, the descriptions of the cyto-

plasm of the rat PSL cells differed considerably from that of PSL cells from the other species studied. Unlike PSL cells of the other studied species, the descriptions of rat PSL cells closely matched descriptions of other ion- and fluid-transporting cells, such as renal tubule cells and ciliary epithelial cells. Consequently, some authors inferred a primary role of PSL cells in the microhomeostasis of inner ear fluids.¹¹⁻¹³

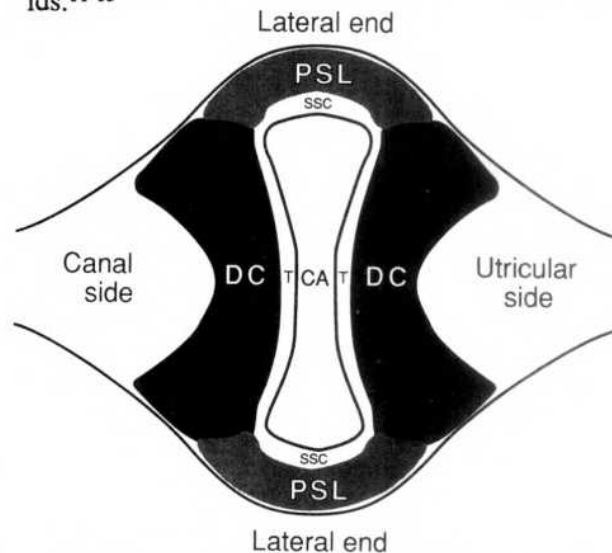


Fig 1. Diagram of different cell regions within ampulla. Region of planum semilunatum (PSL) cells is located at each lateral end of crista ampullaris (CA). DC — dark cells, SSC — sensory supporting cells, T — transitional cells.

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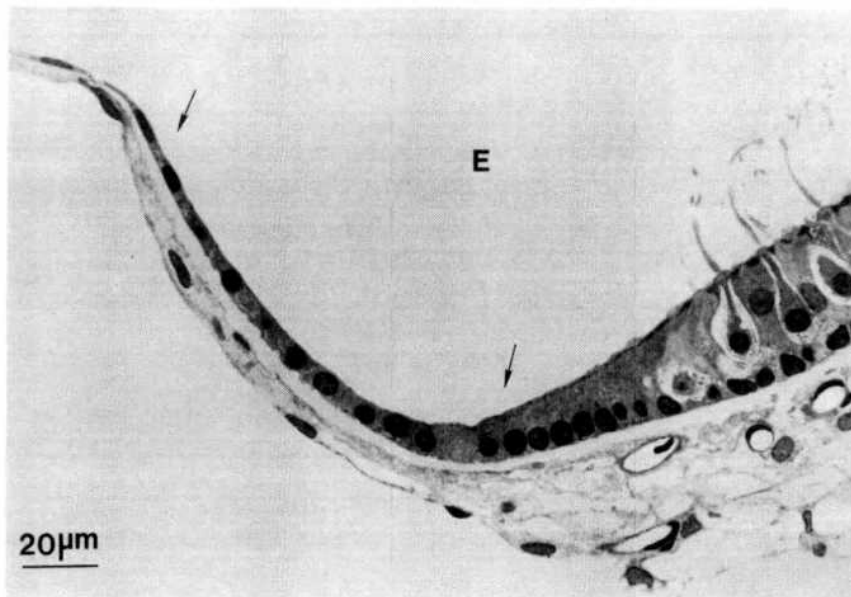


Fig 2. Photomicrograph of lateral end of ampulla (light microscopy, methylene blue stain). Boundary between sensory supporting cells of crista and planum semilunatum region near crista ampullaris, and boundary between planum semilunatum region and squamous epithelial lining cells near ampullar roof are indicated by arrows. Cells of planum semilunatum were observed to be columnar or cuboidal in shape near sensory supporting cells, and to be more flattened in appearance toward ampullar roof. E—endolymph.

It is not clear as of now whether the apparent morphological differences of rat PSL cells as compared to those of other species are a result of an interspecies variation or due to differing past definitions of the PSL. Morphological characteristics of rat PSL cells and other nonsensory epithelia of the rat ampulla, as classified by Dohlman^{6,7} and Kimura et al,⁸ were studied to address this important issue.

MATERIALS AND METHODS

Albino Sprague-Dawley rats (animal farm, University of Florida, Gainesville, Fla; male, 250 to 300 g) and pigmented Long-Evans rats (Charles River, Wilmington, Mass; male, 250 to 300 g) were intramuscularly anesthetized with Ketalar (88.0 mg/kg body weight, Parke-Davis, Morris Plains, NJ) and Rompun (13.0 mg/kg body weight, Mobay Corp, Shawnee, Kan). Each animal was infused via cardiac puncture with 25 mL of cacodylate buffer, pH 7.4, followed by 36 mL of fixative (2.5% glutaraldehyde, 2.5% paraformaldehyde in cacodylate buffer). Temporal bones were removed following painless decapitation, and each bulla was opened. The bony labyrinth overlaying the posterior wall of the utricle and superior and lateral ampullae was removed, and fresh fixative was gently perfused onto the vestibular end organs. Each specimen was submerged in fresh fixative for 1 additional hour, rinsed three times in cacodylate buffer, and post-fixed for 1 hour in cacodylate-buffered 1% osmium tetroxide, pH 7.4. Temporal bones were rinsed three times in cacodylate buffer and dehydrated in graded concentrations of ethanol up to a concentration of 70%. Ampullar tissues of the superior, lateral, and posterior semicircular canals were carefully dissected and removed with the aid of a binocular dissecting microscope. The individual

ampullar tissues were completely dehydrated. All tissues were maintained at 4°C during processing.

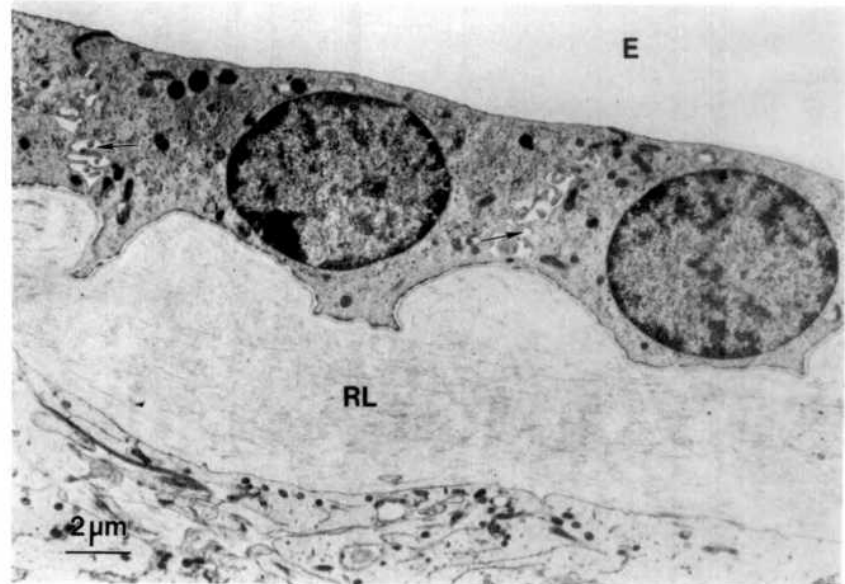
Half of the ampullar tissues from each animal were embedded in Epon-araldite epoxy resin (Polysciences, Warrington, Pa) by means of routine procedures. The ampullar tissues were sectioned at various angles on a Reichert-Jung ultramicrotome with a Diatome MT401 diamond knife, and thick (1 μm) and ultrathin (70 nm) sections of the PSL and other nonsensory epithelia of the ampulla were obtained. Thick sections were stained with methylene blue and observed under a Zeiss Axiophot light microscope. Ultrathin sections were stained with uranyl acetate and lead citrate and examined in a JEOL 100S transmission electron microscope.

The other half of the ampullae were dried in a Denton DCP-1 critical point dryer, with carbon dioxide employed as the transition fluid. Following drying, specimens were mounted on scanning electron microscope stubs and coated with gold-palladium in a Technics Hummer I sputter-coater. Tissues were studied in a JEOL JSM-35C scanning electron microscope.

RESULTS

Light and Transmission Electron Microscopy. Regions of PSL cells were identified in each ampulla at the lateral ends of a crista ampullaris. Cells of the PSL most adjacent to the sensory supporting cells of the crista ampullaris were columnar to cuboidal in shape. The PSL cells appeared more flattened further away from a crista, and they were finally replaced by squamous epithelial cells toward the ampullar roof (Fig 2). The transition between PSL cells and sensory supporting cells was gradual, as was the transition

Fig 3. Representative electron micrograph of region of planum semilunatum cells (uranyl acetate and lead citrate stain). Distinctive features of planum semilunatum cells were lateral plasma membrane infoldings, undulating contours of basal membrane, and thick subepithelial reticular layer. Cytoplasmic process can be seen to protrude into subepithelial reticular layer (RL; left). Arrows — intercellular space between lateral plasma membrane infoldings, E — endolymph.



from PSL cells to cells of the ampullar roof.

The PSL cells were interdigitated with one another by lateral infoldings. Junctional complexes and desmosomes were observed along the lateral membranes of the PSL cells. Many junctionlike contacts were observed between the basal membrane of the PSL cells and the basal lamina. The basal cell membrane did not form infoldings. A continuous basal lamina together with the subepithelial reticular layer was undulating in appearance and formed wartlike impressions in the basal part of the PSL cells. The subepithelial reticular layer was thick (4 to 9 μm) and was composed of many longitudinal and transverse filaments. Occasionally, cytoplasmic processes of PSL

cells protruded into the thick subepithelial reticular layer (Figs 3 and 4).

The nuclei within the PSL cells were circular to oval in appearance and were basally or centrally located. Each nucleus contained predominantly euchromatin. Small mitochondria, rough endoplasmic reticulum, prominent Golgi complexes, and lysosomes were seen in the cytoplasm of the PSL cells. Dark and light granules and several vesicles were observed in the apical cell part of each PSL cell (Fig 3).

The fibrous tissue underlining the PSL contained capillaries, while nerves and melanocytes were absent. Between the albino and pigmented animals, no differences in the ultrastructure of PSL cells were observed by light and transmission electron microscopy.

The PSL cells were distinct from ampullar dark cells that were located on the canal and utricular side of a crista ampullaris, and that appeared also characteristically more electron-dense and contained many basolateral plasma infoldings (Fig 5A). Conversely, similar morphological characteristics were observed in cells of the PSL and those in the transitional regions. For example, both cell types were columnar to cuboidal in shape and interdigitated with lateral infoldings; in both, junctionlike contacts were present between the basal lamina and the basal cell membrane. The thick reticular layer with modifications like those observed in the PSL region was noticeably absent in the transitional cell region (Fig 5B).

Scanning Electron Microscopy. Individual cells of the PSL regions at the lateral ends of each crista ampullaris appeared as irregular-shaped pentagonal or hexagonal cells. Few short microvilli were observed

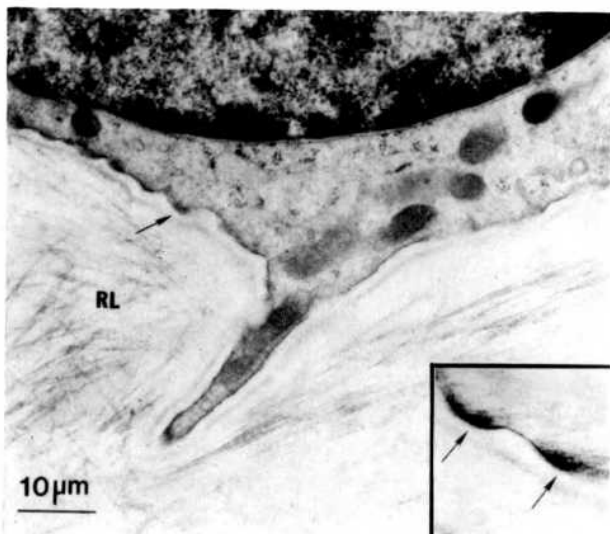


Fig 4. Electron micrograph of basal portion of planum semilunatum cell. Cytoplasmic process is observed to be extending into subepithelial reticular layer (RL). Junctionlike contact (arrow) is observed between basal cell membrane and basal lamina. Inset) Higher magnification of two junctionlike contacts.

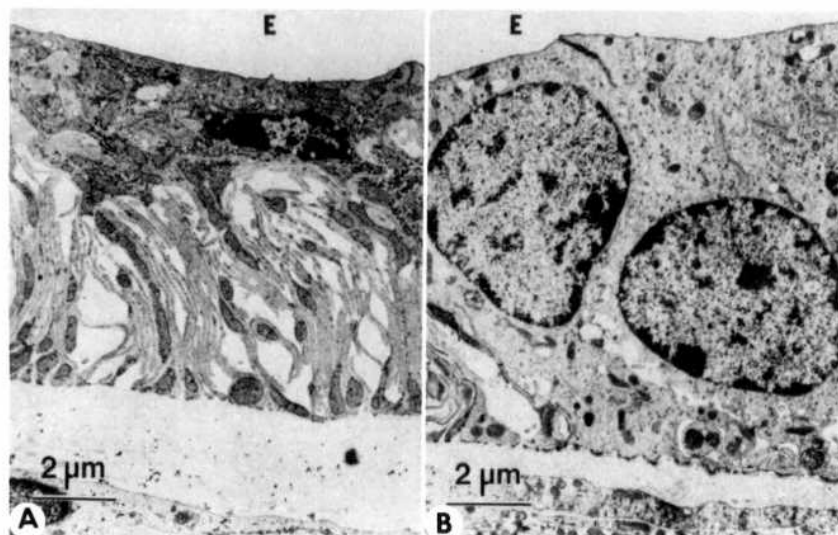


Fig 5. Representative electron micrographs of A) ampullar dark cell region and B) ampullar transitional cell region. Dark cells were observed to be polarized. Whereas innumerable plasma membrane infoldings were located basolaterally, vacuoles and nucleus were located more apically. Transitional cells had many morphological characteristics similar to those of cells of planum semilunatum. However, subepithelial reticular layer of transitional cell region appeared relatively thin compared to that of planum semilunatum cells, and it did not have undulated appearance observed in planum semilunatum cell region. E — endolymph.

on the uneven, slightly convex apical surfaces of the PSL cells. The PSL cells were easily distinguished from the ampullar dark cells, transitional cells, ampullar roof cells, and sensory supporting cells. Rows of microvilli along the cell linings were typical for cells of the transitional region. Dark cells were distinct because the apical surface contained many microvilli, and otoconia were distributed over the dark cell region, although not each individual dark cell contained otoconia on its surface. Rows of microvilli and otoconia were absent on PSL cells (Fig 6). The ampullar roof cells appeared as regular-shaped elongated cells, and the sensory supporting cells contained many short and long microvilli.

The PSL regions were bordered by 1) dark cells and transitional cells on both the canal and utricular sides of the ampulla, 2) vestibular squamous epithelial lining cells toward the ampullar roof, and 3) sensory supporting cells toward the crista ampullaris. The transition from PSL cells to the ampullar dark cells was abrupt. The change from PSL cells to the transitional cells, sensory supporting cells, and roof cells was less precipitous. As with light and transmission electron microscopy, no differences were observed by scanning electron microscopy between PSL cells of the albino animals and those from pigmented animals.

DISCUSSION

Cells of the rat PSL and other nonsensory epithelia of the rat ampulla were observed in this study to be distributed according to the classification of Dohleman^{6,7} and Kimura et al⁸ (Fig 1). Regions of PSL cells were easily distinguished from other nonsensory epithelia at the lateral ends of the crista ampullaris. Individual rat PSL cells can be best described as being irregular-shaped cells that vary in cell height and that

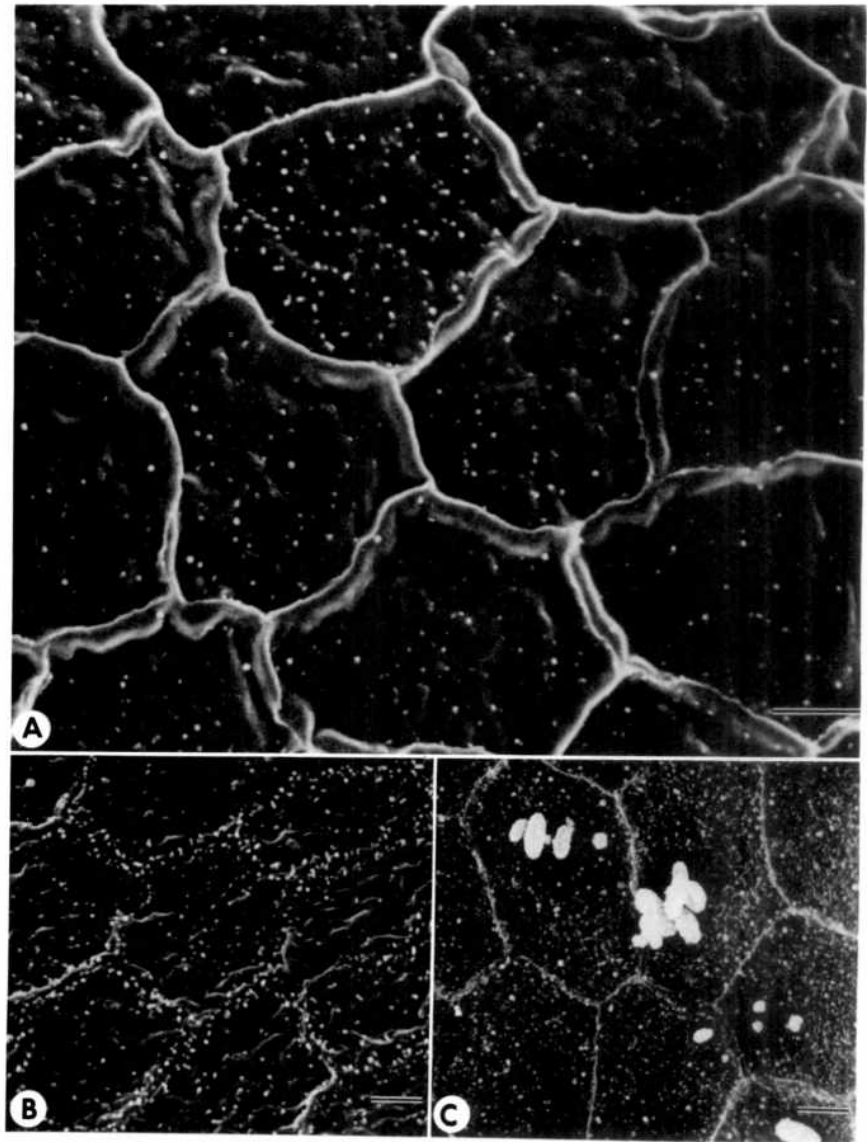
form mainly lateral cell membrane infoldings.

In addition to the distinct cell shape irregularity of the PSL cells, there were other remarkable morphological characteristics of the rat PSL tissues. These included the undulated subepithelial reticular layer and basal lamina that formed wartlike impressions in the PSL cells. There were many junctionlike contacts between the basal lamina and the basal cell membrane. The subepithelial reticular layer was distinctly thick, and individual processes of a PSL cell extended occasionally into clefts of the subepithelial reticular layer.

Interpretation of the role of this uniquely shaped thick subepithelial reticular layer remains speculative. In general, one function of connective tissue is to maintain the structural integrity of tissues. Similarly, the subepithelial reticular layer of connective tissue is thought to play a supportive role.¹⁴ The protrusions of the subepithelial reticular layer into PSL cells increase the contact area between PSL cells and subepithelial reticular connective tissue. This phenomenon of enlarged contact area between epithelium and connective tissue is thought to strengthen the junction between these two layers, since it has been typically observed in tissues that are under mechanical stress, eg, skin and gingiva.¹⁵ In these epithelia the subepithelial connective tissue forms papillae that protrude into the epithelial layer. Presence of these modifications of the basal lamina and reticular layer mainly in the PSL region may therefore suggest that PSL cells are under higher mechanical stress than other nonsensory cells. Mechanical stress on the PSL region may be due to its anatomic position between the solidly anchored crista ampullaris and the "free" thin layer of roof cells.

Another possible role of the subepithelial reticular layer of the PSL may be the mediation of transport

Fig 6. Representative scanning electron micrographs of A) planum semilunatum cells, B) transitional cells, and C) ampullar dark cells. Cells of planum semilunatum were irregularly shaped, and only few microvilli were observed on their endolymphatic surfaces as compared to transitional cells and dark cells. Otoconia were observed routinely on apical surfaces of dark cells. Bars — 2 μ m.



processes. The thick reticular layer may slow transport of substances, since the travel distance for their diffusion would be increased. Furthermore, the thick reticular layer may inhibit rapid washout of substances because the close approximation of capillaries is prevented.

The ultrastructure and distribution of the individual rat PSL cells appeared similar to those of the PSL cells in other animal species,^{7,8,10,16} although the dark-stained granules in the rat PSL cells were not as predominant as in the guinea pig and squirrel monkey.^{8,10} Observations of the rat PSL in this study are in marked contrast with former reports on the ultrastructure of the rat PSL cells.¹¹⁻¹³ Earlier studies described the rat PSL cells as being polarized: an apical zone that contained the nucleus, many vesicles and vacuoles, and a basal zone that consisted mainly of double-layered parallel membranes perpendicular to the basal lamina. Such original descriptions of the rat

PSL cells closely resemble descriptions of ampullar dark cells as observed in the present study and previous studies.^{8,17}

Theoretically, the dissimilarity between the earlier observations and the present ones may be due to a different orientation of the ampullae in the sectioning process or to the use of either albino or pigmented rats in the different studies. The original observations could not be reproduced, however, when the ampullar tissues of albino and pigmented rats were sectioned at various angles in this study. It is more plausible that previous reports on the ultrastructure of the rat PSL cells were based on a definition of the PSL that included a cell population of ampullar dark cells.

The function of the PSL is unclear. Based on the original morphological descriptions of rat PSL, a role in fluid and ion transport has been inferred.¹¹⁻¹³ Observations of this study, however, demonstrated that rat PSL cells contain minimal amplification of plasma

membranes and only a few mitochondria as compared to ampullar dark cells. In this respect the ampullar dark cells seemed more active in ion and fluid transport than do PSL cells. The presence of small vesicles and a prominent Golgi complex of PSL cells may indicate secretory activity. Tracer experiments have suggested the secretion of sulfomucopolysaccharides into interfibrillar spaces of the cupula by PSL cells.¹⁸ Certainly, study of a homologous population of PSL cells is necessary in order to delineate their functions. Correct uniform classification and careful

anatomic description provide the basis for further evaluation of these cells.

In conclusion, this morphological study demonstrates that the ultrastructure of the rat PSL cells is morphologically similar to that of the PSL cells of other species as observed by light, scanning, and transmission electron microscopy. Special modifications of the subepithelial layers were observed in the PSL region, and their possible roles were identified in relation to tissue integrity and fluid microhomeostasis.

ACKNOWLEDGMENT — The authors thank Dr Wojciech Pawlina for helpful comments in the preparation of this manuscript.

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EFFECT OF ENDOTOXIN ON CULTURED CHINCHILLA MIDDLE EAR EPITHELIUM

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The effect of endotoxin on the growth and morphology of cultured chinchilla middle ear epithelium was examined. Within 24 hours of culture, cells maintained in medium containing endotoxin exhibited dose-dependent morphological changes. The highest concentration of endotoxin (100 mg) resulted in cell death. The growth curve of the cells in culture demonstrated a dose-dependent, significant increase in cell number when endotoxin was added to the medium.

KEY WORDS — cell culture, endotoxin, middle ear epithelium.

INTRODUCTION

It has been generally accepted that chronic otitis media with effusion (OME) or serous otitis media is causally related to acute otitis media, and that bacteria or their cell wall components may play a pathogenic role in this disease.¹ Three major pathogens are known to be involved in both acute otitis media and chronic OME: *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis*. Of these three, the latter two are gram-negative bacteria that contain endotoxin (lipopolysaccharide) in their outer membrane. Appreciable amounts of endotoxin have been found in middle ear effusions obtained from patients undergoing tympanostomy tube insertion due to OME.²⁻⁵ Endotoxin is a highly potent inflammatory mediator⁶ and even a small amount of it can induce a severe inflammatory response and effusion in the middle ear of chinchillas⁷ or guinea pigs.⁸ These inflammatory responses include extensive proliferation of the chinchilla middle ear epithelium and fibrosis resembling adhesive otitis media.⁹

While the mechanism by which endotoxin induces such cell proliferation is not clear, recent preliminary data obtained from serially cultured rat middle ear epithelium demonstrated that endotoxin stimulates cell proliferation in a dose-dependent manner¹⁰; hence, endotoxin's effect on cell proliferation may be direct. The present investigation was undertaken to assess the effect of endotoxin on serially cultured chinchilla

middle ear epithelium in the hope of elucidating the cellular mechanism involved in this cell proliferation.

MATERIAL AND METHODS

Cell Preparation. Chinchilla middle ear epithelium was prepared from the tympanic bulla and primary explant culture described earlier by Nakamura et al,¹¹ and subsequently these passaged cells were used for the study. The experiments were conducted by two culture techniques: 1) co-culture with feeder cells using regular medium and 2) use of conditioned medium without feeder cells. In the first method, irradiated 3T3 feeder cells were plated at a density of 2.4×10^4 /mL along with epithelial cells maintained in regular medium at a density of 2×10^4 /mL.¹² In the second method, a mixture of equal amounts of the conditioned medium and regular medium was added to the subcultured epithelial cells. The culture dishes used were 24-well tissue culture plates (Falcon). Fourth and seventh passages of chinchilla middle ear epithelial cells were used for this study.

Feeder Cell Preparation. Mouse fibroblast 3T3 cells were rendered mitotically inactive by irradiation with 30 Gy of gamma rays from a Gama cell 40 cesium irradiator (Atomic Energy of Canada Ltd, Ottawa, Canada). These cells were seeded at a density of 2.4×10^4 /mL.

From the Otolological Research Laboratories, Department of Otolaryngology, The Ohio State University College of Medicine, Columbus, Ohio (Nakamura, DeMaria, Lim), and the Laboratory for Otobiology and Biocompatibility, Ear, Nose, and Throat Department, University of Leiden, Leiden, the Netherlands (van Blitterswijk). Dr Nakamura is currently in the Department of Otolaryngology, Kansai Medical School, Osaka, Japan. This study was supported in part by National Institutes of Health/National Institute on Deafness and Other Communication Disorders grant R01 DC00090 and in part by an International Rotary Fellowship to Dr Nakamura. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH Guide for the Care and Use of Laboratory Animals, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of The Ohio State University.

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Culture Medium for Epithelial Cells. A mixture of three parts high-glucose Dulbecco's modified Eagle's medium and one part Ham's F12 supplemented with 5% fetal bovine serum, 0.4 $\mu\text{g/mL}$ hydrocortisone, 10^{-6} mol/L isoproterenol, 100 U/mL penicillin, 100 $\mu\text{g/mL}$ streptomycin, and 10 ng/mL epidermal cell growth factor (EGF; Sigma E41257) was used for serial culture of the epithelial cells.¹¹

Culture Medium for 3T3 Cells. This was prepared as above, but without EGF.

Conditioned Medium. Conditioned medium consisted of the supernatant of 1.2×10^4 irradiated 3T3 cells maintained in culture for 1 week. The supernatants were filter-sterilized prior to use.

Endotoxin. The endotoxin used for this study was prepared from *Salmonella typhimurium* (Sigma, catalog number L6511). It was chosen because of its biologic similarity to the endotoxin derived from nontypeable *Hemophilus influenzae*.¹³

Effect of Endotoxin on Cell Growth. Chinchilla middle ear epithelial cells were grown to confluency in a T-75 flask, trypsinized, and then planted in 24-well tissue culture plates at a density of 2×10^4 cells per well. An equal concentration of 3T3 feeder cells was added to each well. The next day regular media were replaced with medium containing various concentrations of endotoxin. Media containing 0.001, 0.1, 1.0, and 100 $\mu\text{g/mL}$ of endotoxin were added to the appropriate wells. Beginning on the 4th day of culture, EGF was added to the cells in a concentration of 10 mg/mL. Controls received the same media containing EGF. A cell count was performed on the 1st, 4th, 7th, 10th, and 14th days, and fresh endotoxin-containing medium was added to the cells on each evaluation day. The number of cells in each of three wells at each concentration of endotoxin was counted by the trypan blue dye exclusion method using a Neubauer hemocytometer, and a growth curve was made from the average value of the triplicate counts. Cells were examined with a phase contrast microscope (Zeiss ICM405) and photographed on each evaluation day.

In separate experiments, conditioned medium was used instead of 3T3 feeder cells. Also, in a separate experiment, the chinchilla middle ear epithelial cells were mixed in suspension with endotoxin prior to plating.

Statistics. Data were determined by calculating the arithmetic mean and standard deviation based on three replicates at each endotoxin concentration. Observations are assumed to be approximately normally distributed, and Student's *t* test was used to

determine the difference between means. We selected a $p \leq .01$ level of significance for all analyses.

RESULTS

Results obtained with 3T3 feeder cells or conditioned medium were essentially identical in cell response to endotoxin. The cells cultured with or without feeder cells in endotoxin medium established cell attachment on the fourth day after plating (Fig 1A) and reached confluency by day 10 (Fig 1B). Control cultures maintained with 3T3 feeder cells or conditioned medium showed normal cobblestone formation (Fig 1A). There were no morphological differences between those cultures with endotoxin in the media and those in control medium within 24 hours of exposure to the endotoxin. After 24 hours in culture, cells maintained in the media with endotoxin levels below 0.1 μg of endotoxin maintained relatively normal gross morphology (Fig 1C), whereas those maintained in medium containing 1 μg of endotoxin showed areas of cell detachment in patches surrounded by normal-appearing epithelial cells (Fig 1D). High concentrations (eg, 100 μg) of endotoxin appeared to cause cell injury and cell death in culture. Many dead cells were found detached from the Petri dish and floating by day 4, and those that remained attached were highly granular and appeared abnormal (Fig 2A). This abnormality persisted throughout the experiment (Fig 2B).

The growth curve of the cells in culture demonstrated that a dose of 1 $\mu\text{g/mL}$ of endotoxin induces a statistically significant proliferation ($p \leq .01$) of the cells at 4 and 7 days when compared to controls without endotoxin (Fig 3). A dose of 0.1 $\mu\text{g/mL}$ induces a statistically significant increase ($p \leq .01$) in cell number by 10 days in culture. Concurrently, the 100- $\mu\text{g/mL}$ concentration of endotoxin resulted in cell death and a proliferation rate much less than that observed in the control cultures throughout the duration of the experiment. There were fewer cells present at the 100- μg concentration for the duration of the experiment compared to the control cells, and the decline in the number of cells at the 100- $\mu\text{g/mL}$ concentration was statistically significant at day 7 and day 14.

DISCUSSION

The present study was mainly motivated by our previous observation that nonviable *H influenzae* or endotoxin purified from this organism, when introduced into the bulla of the chinchilla, resulted in an extensive inflammatory response accompanied by abnormal proliferative changes in the epithelium and in the subepithelial tissue.^{7,9} Such epithelial prolifer-

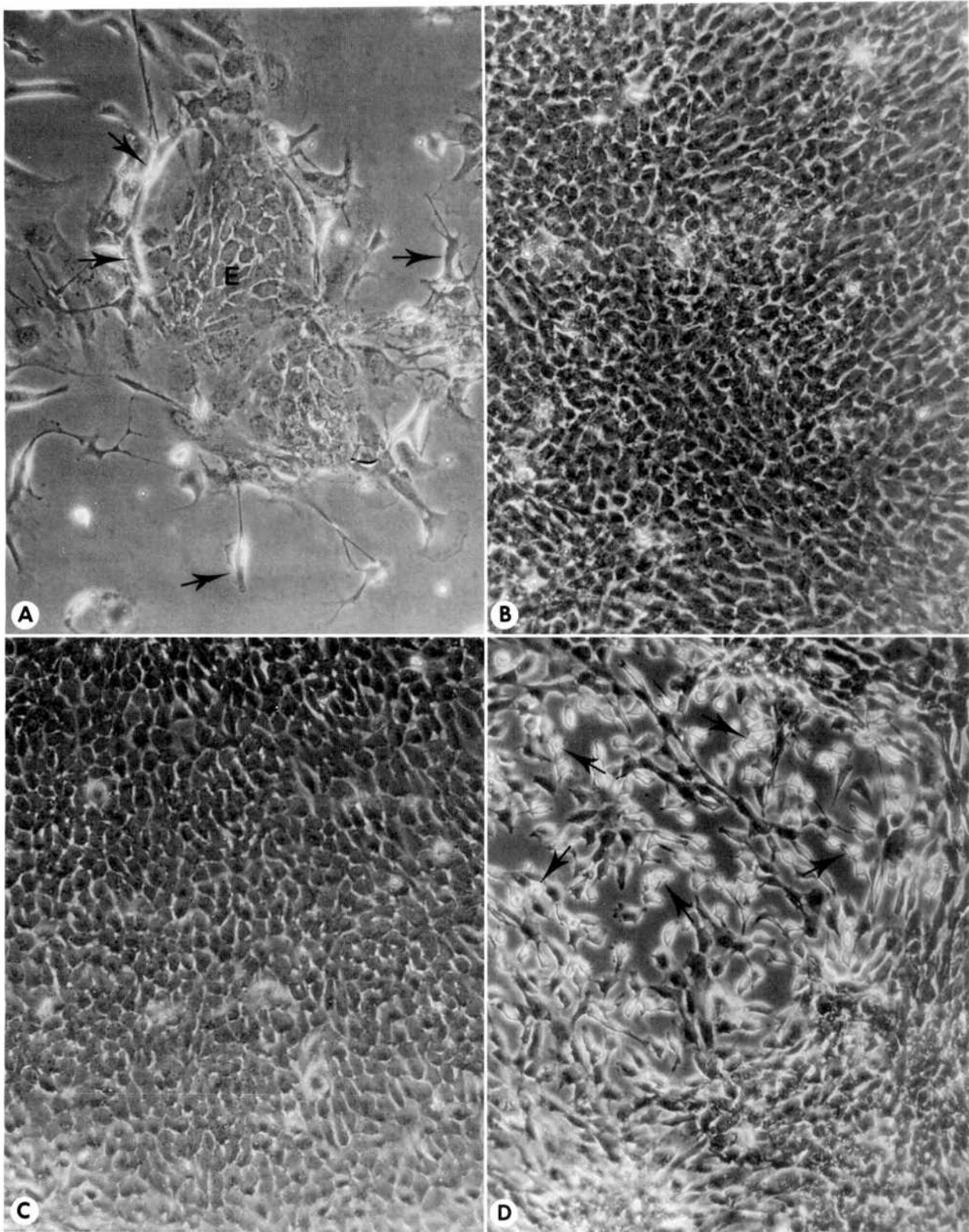


Fig 1. Phase-contrast light micrographs (original $\times 125$). A) Chinchilla middle ear epithelial cells (E) in endotoxin-free medium on fourth day in culture maintained with 3T3 feeder cells (arrows). B) Epithelial cells in control (endotoxin-free) medium after 10 days in culture. Typical cobblestonelike monolayer of epithelial cell growth was seen. C) Epithelial cells in medium containing low dose (0.1 $\mu\text{g/mL}$) of endotoxin after 10 days. These cells also showed cobblestonelike monolayer formation similar to cells cultured in control medium without endotoxin. D) Epithelial cells in medium containing 1 $\mu\text{g/mL}$ of endotoxin after 10 days. Many cells showed signs of deterioration and cell death resulting in cell detachment (arrows).

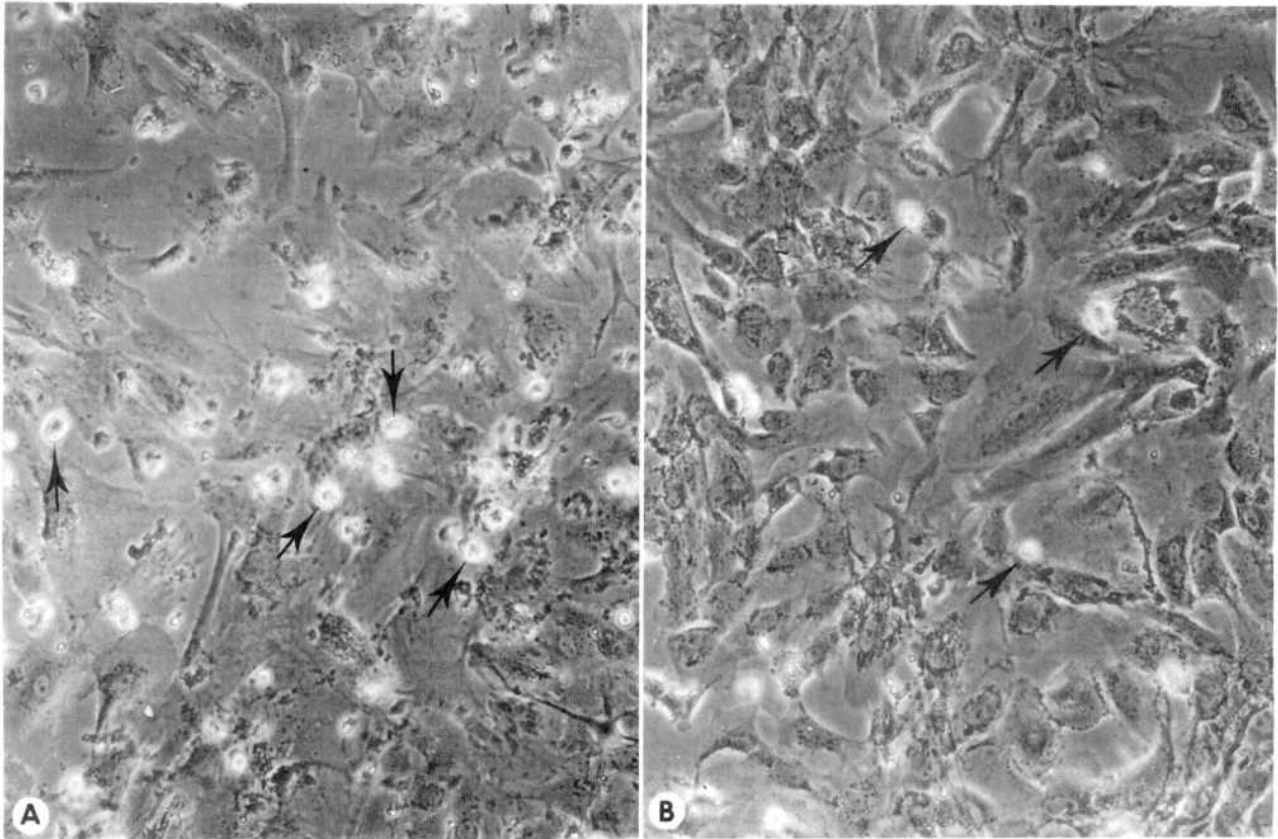


Fig 2. Phase-contrast light micrographs (original x125). A) Passage 7 epithelial cells in medium containing 100 µg/mL of endotoxin after 4 days in culture. Cells that survived were highly granulated and failed to show cobblestone features. Many cells show signs of cell degeneration and cell death. Dead cells became detached and floating (arrows). B) Epithelial cells cultured in medium containing 100 µg/mL of endotoxin, shown after 10 days in culture. Cells remained highly granular and appeared abnormal, and many cells are detached because of degeneration or cell death (arrows). Cobblestone appearance of typical cultured epithelial cells is not seen.

erative response was far greater than that seen after injection with nonviable pneumococci.⁷ While the underlying mechanism(s) for such proliferative changes is unknown, one possibility may be the direct endotoxin effect on the middle ear epithelial cells.

A recent preliminary report by van Blitterswijk et al¹⁰ suggests a dose-dependent, endotoxin-induced proliferation of rat middle ear epithelium. The chinchilla middle ear epithelium does exhibit this response, but appears more sensitive than that of the rat to the toxic effects of endotoxin and less responsive

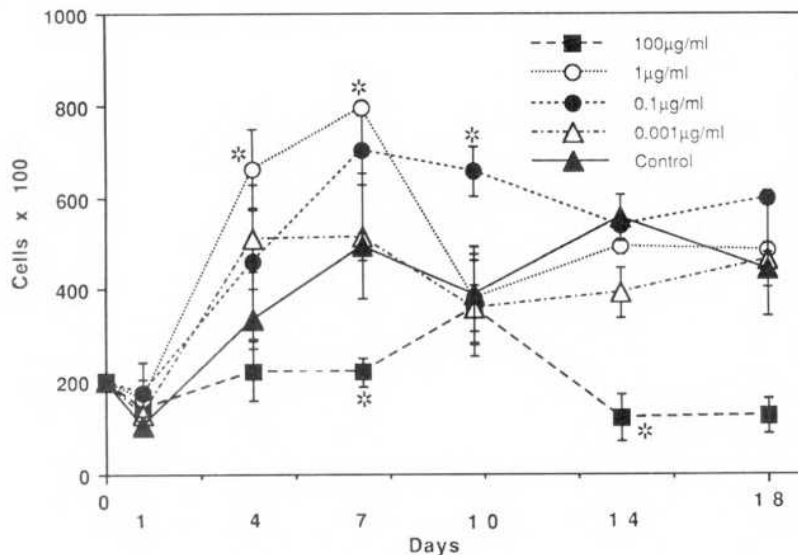


Fig 3. Growth curve of chinchilla middle ear epithelial cells exposed to graded doses of endotoxin. Each data point represents arithmetic mean of cell counts from three separate wells. Data points marked with asterisk are statistically significant ($p \leq .01$).

to the proliferative effects. Chinchilla cells responded to a narrower concentration range than rat cells. The highest dose (100 µg) inhibited chinchilla epithelial cell growth and was toxic, but this same dose stimulates proliferation of and is not toxic to rat epithelial cells.¹⁰

Species differences could account for the differential response observed between the two species, because our initial concern, that differences in the time and method of adding endotoxin to the cultures could account for the disparity, did not prove true. The growth curve of the chinchilla middle ear epithelium was the same regardless of whether the endotoxin was mixed with the cells prior to plating¹⁰ or whether it was added to the cultures 24 hours after cells were planted and attached, as in the present study.

Sugita et al,¹⁴ using keratinocytes derived from the epidermis of newborn rat skin, demonstrated the effect of endotoxin on the growth of the keratinocytes

by measuring the rate of DNA synthesis using ³H-thymidine incorporation. Either endotoxin or prostaglandin E₂ alone inhibited DNA synthesis by keratinocytes, while endotoxin (10 µg/mL) and prostaglandin E₂ (10 ng/mL) together stimulated DNA synthesis by keratinocytes. Their data suggest that it is possible that the proliferative effects of endotoxin on the chinchilla middle ear epithelium in vivo might require the presence of other factors, such as prostaglandin E₂, as well.

Another possibility is that the epithelial cell death caused by endotoxin may enhance the proliferation of the basal cells, leading to the piling-up phenomenon observed in the chinchilla after endotoxin bullar instillation. It is also possible that growth factors may have been produced by the epithelial cells or cells in the connective tissue by endotoxin toxicity, leading to the proliferation of the epithelial cells. Further study is needed to answer these questions.

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VESTIBULAR PATHOPHYSIOLOGIC CHANGES IN EXPERIMENTAL PERILYMPHATIC FISTULA

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An animal model of experimental perilymphatic fistula (EPLF) was developed in the guinea pig in order to study vestibular pathophysiology. In experimental animals, 4 μ L of perilymph was suctioned from one cochlea via the round window membrane. Changes in vestibular function were as follows. 1) During the acute stage (5 hours postoperatively), spontaneous nystagmus directed toward the normal side was noted in 57.4% of the EPLF animals. This lasted less than 24 hours. 2) One week postoperatively, direction-fixed positional nystagmus toward the lesioned ear was present in 22.7% of the EPLF animals, especially when the lesioned ear was positioned inferiorly. 3) With the ice water caloric test, no response was present in 58.1% of the EPLF animals and an irregular response was found in 22.6% of them, 1 week postoperatively. These results tend to indicate that tests of vestibular function may differentiate between patients with Meniere's disease and those with perilymphatic fistula. Histologic findings indicate that a floating labyrinth is the cause of positional nystagmus and caloric irregularity. The absence of caloric responses was associated with collapse of the vestibular labyrinth.

KEY WORDS — caloric test, experimental perilymphatic fistula, floating labyrinth, vestibular atelectasis.

INTRODUCTION

Perilymphatic fistula (PLF) may occur in either the round or the oval window, permitting leakage of perilymph from the inner ear into the middle ear cavity. The leakage of perilymph is associated with a variety of symptoms such as vertigo, tinnitus, and hearing loss. At present, there is no reliable test to diagnose this condition preoperatively.

Recently in our clinical practice, more and more cases that initially appeared to be Meniere's disease have been subsequently shown to be PLF at exploratory tympanotomy. Thus, a misdiagnosis of Meniere's disease in patients with PLF may occur quite frequently.

In previous animal experiments,^{1,2} we were able to induce endolymphatic hydrops by creating a PLF. The association of hydrops with both these disease entities may be responsible for the diagnostic dilemma of otolaryngologists. In addition, there is limited information about the vestibular portion of the inner ear in experimental perilymphatic fistula (EPLF), although some reports^{3,4} discuss it from an audiological perspective.

The aim of the present study was to determine the vestibular pathophysiologic findings in EPLF and to attempt to clarify the confusion between Meniere's disease and PLF from the vestibular point of view.

MATERIALS AND METHODS

Seventy-two normal albino guinea pigs weighing

200 to 350 g were used in this study. Under intraperitoneal pentobarbital sodium anesthesia (40 mg/kg), the left tympanic bulla was opened to expose the round window area. With a microsyringe, a volume of 4 μ L of perilymph was suctioned from the cochlea via the round window membrane to create an animal model of EPLF (n = 66).

For comparative study, instrumental puncture of the round window membrane was performed in six animals without suctioning perilymph.

None of the operated round window membranes were sealed after either procedure. In all animals, only the left ear was operated on; the right ear served as an unoperated control. Aside from the initial 12 animals, the rest of the animals were closely observed at 5 and 24 hours postoperatively for the presence of spontaneous nystagmus.

At 1 and 2 weeks postoperatively, vestibular function was tested in all animals by using electro-nystagmographic (ENG) recordings.⁵ The presence of spontaneous nystagmus and positional nystagmus was determined, as well as the response to ice water calorics.

For the vestibular function tests, the guinea pig was restrained in a special holder, with its four legs free. A pair of clip electrodes was attached to the canthi of both temporal orbits, and a reference electrode was attached to the vertex at the midline.⁵ The use of anesthetic, hair shaving, and surgical invasion were not required for ENG recording. For the caloric test, 5 mL of ice water (0°C) was used to

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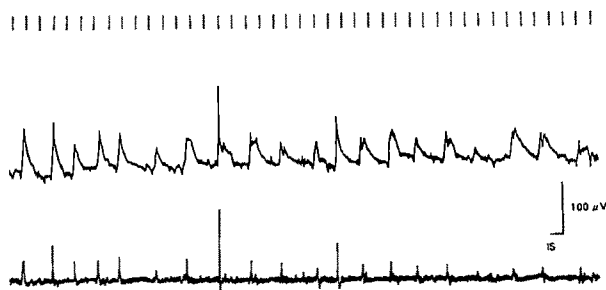


Fig 1. Electronystagmograph recording of spontaneous nystagmus in experimental perilymphatic fistula animal (left) 5 hours postoperatively. Top trace is time base at 1 mark per second. Second trace is eye movement (nystagmic movement). Third trace is differentiated eye movement showing eye velocity.

irrigate the ear canal for 5 seconds, with the animal in the normal prone position. Recordings were made with a two-channel ENG recorder (NY-13 Rion Co, Tokyo, Japan).

After ENG recordings were completed, the animal was deeply anesthetized (pentobarbital sodium, 50 mg/kg intraperitoneally) and perfused intravitaly with normal saline and Heidenhain-Susa fixative. The temporal bones were then removed after decapitation and processed for histologic study by using the conventional celloidin technique. The specimens were serial sectioned at a thickness of 15 μ m and every 10th section was stained with hematoxylin and eosin and examined microscopically.

RESULTS

The animals recovered from anesthesia after an average of 5 hours. At that time, right-beating spontaneous nystagmus was present in 31 of 54 (57.4%) EPLF animals (Fig 1), and these animals also exhibited head tilt to the side of the lesion. The spontaneous nystagmus disappeared within 24 hours of the operation and did not recur.

Direction-fixed positional nystagmus was detected in 15 of 66 (22.7%) EPLF animals 1 week postoperatively. This positional nystagmus was directed toward the experimental ear, in particular when it was positioned inferiorly. However, positional nystagmus was absent in all EPLF animals 2 weeks after the operation.

The interpretation of the ice water caloric test was based on the normal caloric response of the control ear. Animals in which the control ear did not have normal caloric responses ($n = 4$, owing to animal noncooperation) were excluded from the caloric study. At 1 week postoperatively, 36 of 62 animals (58.1%) had no caloric response in the lesioned ear (Fig 2); 14 (22.6%) revealed caloric irregularity (Fig 3); and 12 animals had normal caloric responses. Thus, 50 of 62 animals (80.6%) had an abnormal response to the ice water caloric test 1 week postoperatively.

Six of the 36 animals with canal paresis showed a

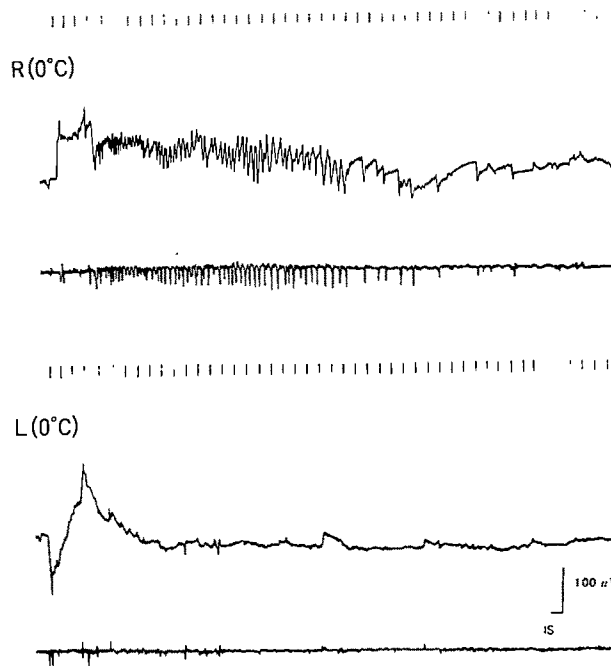


Fig 2. Electronystagmograph recordings in response to ice water caloric test in experimental perilymphatic fistula animal, 1 week postoperatively. Right (control) side shows normal caloric response, whereas left (experimental perilymphatic fistula) side shows no response. Traces are same as in Fig 1.

return of vestibular function as measured by the ice water caloric test 2 weeks postoperatively (Fig 4). The caloric responses of the remaining animals remained the same as the first week.

The six animals (comparative group) that underwent round window membrane puncture without suctioning perilymph had neither spontaneous nor positional nystagmus, and their response to the caloric test was normal 1 week following the operation.

The morphologic changes in the temporal bones of the EPLF animals have been described in part recently,⁶ the principal finding in the vestibular system being collapse of the vestibular labyrinth (Fig 5).

In the animals with no caloric responses, collapse of the membranous labyrinth in the utricle and ampullae was noted. The membranous labyrinth covered the top of the crista ampullaris, appearing as "vestibular atelectasis."⁷ In animals with caloric irregularities, a "floating labyrinth"⁶ was detected; that is, partial collapse of the membranous labyrinth with some tearing of the trabecular meshwork. The sensory cells, vestibular ganglion cells, and nerve fibers remained intact during the 2-week period.

Animals in which the caloric responses returned by 2 weeks had a normal contour of the lateral ampulla but a mild collapse of the utricular wall (Fig 6).

DISCUSSION

Simple rupture of the labyrinthine window can-

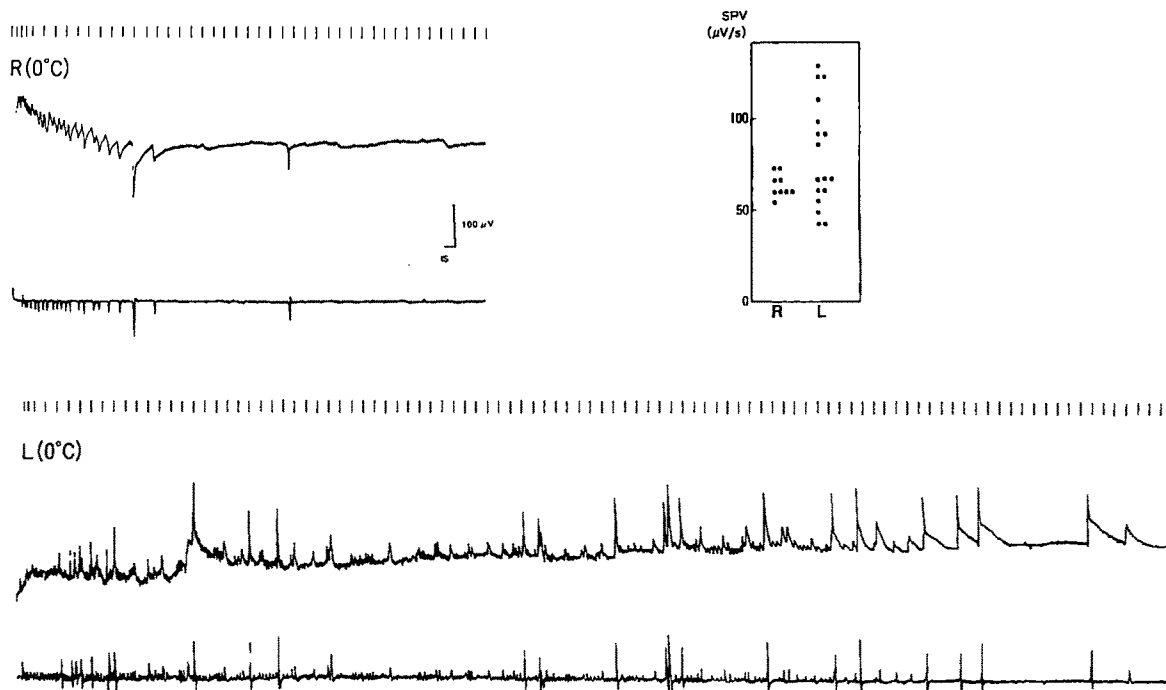


Fig 3. Prolonged caloric irregularity lasting 98 seconds with variable slow-phase velocity (SPV) in left ear of experimental perilymphatic fistula animal, 1 week postoperatively. Right side shows controlled caloric response, with 14-second duration and constant SPV. Column shows SPVs calculated from electronystagmograph recordings of conventional nystagmus curves. Traces are same as in Fig 1.

not explain the variable clinical picture of PLF. Therefore, the association of PLF with a morphological or physiologic deficiency in the membranous labyrinth is a generally accepted view. Factors leading to round window membrane rupture are important in the explanation of the signs and symptoms of PLF. Using animal experiments to elucidate the pathophysiology of PLF will compensate for the lack of human temporal bone studies in this area.⁸

In previous studies, we established two animal models of EPLF, using a perilymph injection method¹ and a perilymph suction method.² There is no significant difference in the morphological changes in the membranous labyrinth following use of either of these methods. Therefore, either the injected animal or the suctioned animal can be used to create an animal model of EPLF in order to study its pathophysiology.

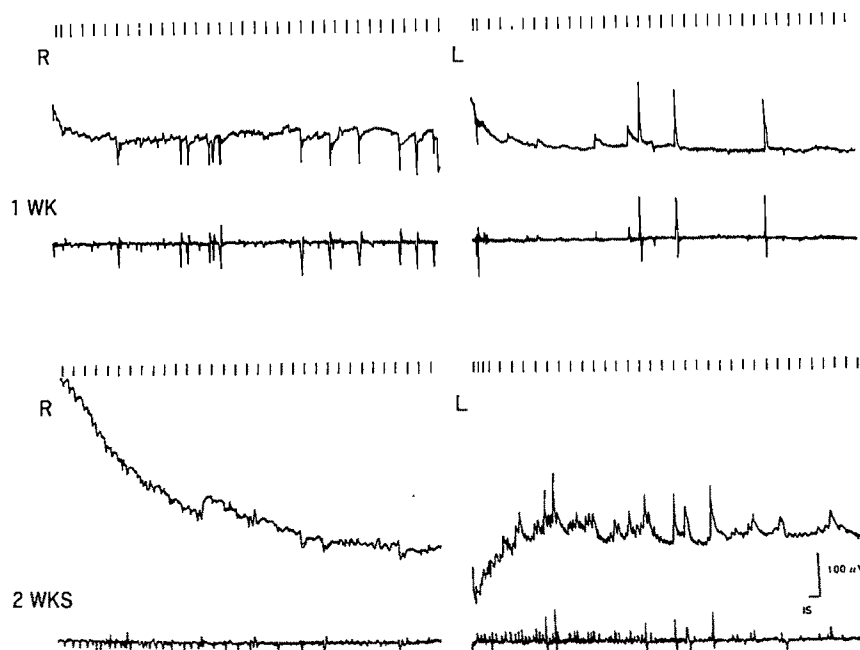
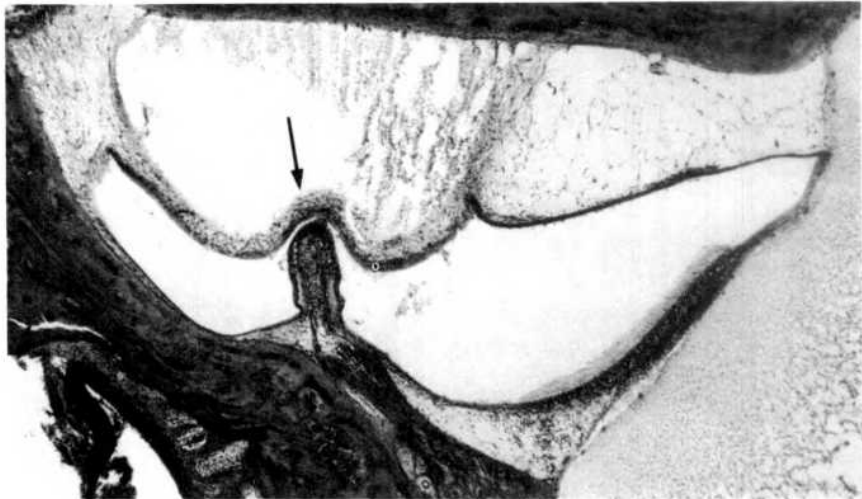


Fig 4. Return of vestibular function can be seen at 2 weeks postoperatively in experimental perilymphatic fistula ear. Canal paresis is present in left ear 1 week postoperatively, but normal responses have returned by 2 weeks. Right side shows controlled caloric responses. Traces are same as in Fig 1.

Fig 5. Experimental perilymphatic fistula animal with canal paresis, 2 weeks postoperatively (original x25). Collapsed membranous labyrinth of lateral semicircular canal covers crista ampullaris (arrow). Marked precipitate is present in perilymphatic space.



When PLF occurs, a simultaneous lesion such as collapse of the vestibular labyrinth may also occur in the membranous labyrinth, resulting in the deprivation of peripheral vestibular inputs. The latter condition provokes spontaneous nystagmus, called "paralytic nystagmus,"⁹ that is directed to the intact side. Paralytic nystagmus lasts less than 24 hours and then disappears, probably because of central compensation.

Positional nystagmus is thought to be a diagnostic symptom in PLF patients; however, its mechanism remains to be clarified.

In both human patients and EPLF animals, positional nystagmus is directed toward the side of the lesion, particularly when the affected ear is positioned inferiorly. Positional nystagmus may occur because of a disturbance in the interaction between the otolithic organs and the semicircular canals due to altered movement of the inner ear fluids. The partially collapsed membranous labyrinth is adherent to the otolith of the utricular macula and the crista ampullaris.⁶ Perilymph flow may force the collapsed membranous labyrinth to sway, thereby stimulating the sensory cells. One can speculate that

the phenomenon of the floating labyrinth may be responsible for the persistent unsteadiness and positional nystagmus seen in PLF patients.

In EPLF animals, positional nystagmus disappeared during the 2-week postoperative period. This situation differs from what is observed in patients and may be explained by the rapid healing that occurs in the ruptured round window membrane in guinea pigs (Fig 7). This result also suggests that surgical repair in PLF patients will be successful in relieving their vestibular symptoms.

A total of 58.1% of EPLF animals showed no response to the ice water caloric test. The underlying pathogenesis was demonstrated to be total collapse of the membranous labyrinth in the lateral semicircular canal (Fig 5). If the membranous labyrinth only partially collapses, irregular perilymphatic flow will interfere with the movement of endolymph to still-viable sensory organs, resulting in an irregular caloric response, which was detected in 22.6% of the EPLF animals.

The term caloric irregularity refers to a gross irregularity in the amplitude and/or frequency of ca-

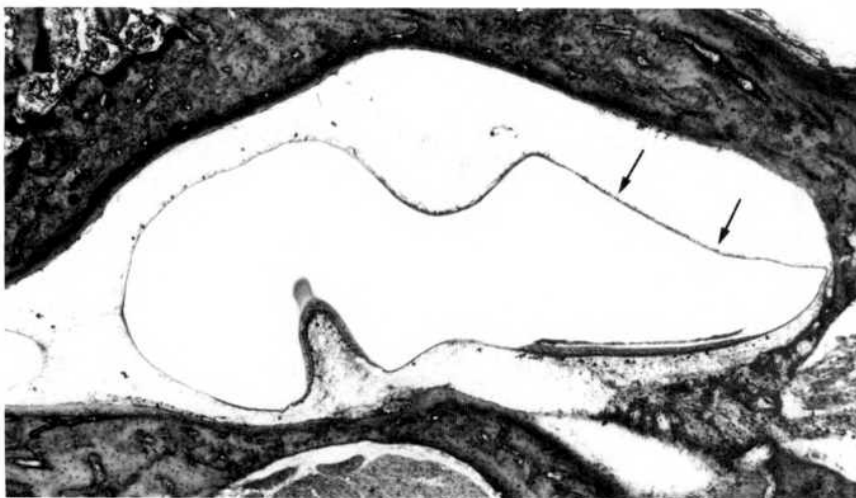


Fig 6. Experimental perilymphatic fistula animal that had return of caloric response in left ear 2 weeks postoperatively (original x25). No collapse is seen in lateral ampulla. Utricle wall shows mild collapse (arrows).



Fig 7. Healing of ruptured round window membrane (arrows) in left ear of experimental perilymphatic fistula animal 2 weeks postoperatively (original x10). ST — scala tympani.

loric nystagmus with a variable slow-phase velocity, compared to the control side. Interestingly, the duration of irregular caloric response was always longer for the lesioned ear than for the control ear in our EPLF animals (Fig 3). Caloric irregularity in vestibular atelectasis patients has also been described by Merchant and Schuknecht.⁷ They reported that patients with partial collapse of the walls of the ampullae and utricle have continuous nystagmus in response to caloric stimulation. This pathologic condition is identical to what is known as a floating labyrinth. The similar pathologic findings in patients and experimental animals suggest a causal relationship between caloric irregularity and a floating labyrinth.

Caloric responses may return in some PLF patients after surgical repair. This phenomenon was also observed in six EPLF animals that had a normal contour or very mild collapse of the membranous labyrinth 2 weeks postoperatively. This implies that vestibular function alterations are reversible as long as the contour of the vestibular membranous labyrinth and the sensorineural elements are preserved.

Thus, the evolution of nystagmus in EPLF, with spontaneous nystagmus directed to the normal side

(paralytic nystagmus) that disappeared after 24 hours followed by positional nystagmus directed to the lesioned side, is opposite to that seen in most cases of Meniere's disease. It is well known that during most acute attacks of Meniere's disease, the nystagmus beats to the lesioned side (irritating nystagmus) and then changes to nystagmus directed away from the lesion (paralytic nystagmus) during the convalescent stage. This difference in the pattern of evolution of nystagmus for PLF and Meniere's disease may be a useful diagnostic aid to differentiate clinically between these two disease entities.

In addition, the absence of caloric responses or caloric irregularity is rarely seen in patients with Meniere's disease. An absent or irregular response to the ice water caloric test may also serve as a means of differentiation.

In conclusion, recognition of the vestibular pathophysiologic changes such as spontaneous nystagmus, positional nystagmus, and absent or irregular response to the ice water caloric test in EPLF animals was used to determine the nature and side of the lesion. We recommend the use of vestibular function tests to aid in the differential diagnosis between Meniere's disease and PLF.

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IMAGING CASE STUDY OF THE MONTH

CARTILAGINOUS TUMOR OF THE LARYNX

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CASE REPORT

The patient was an 80-year-old woman who presented with complaints of exertional dyspnea and progressive hoarseness. She reported having had an inability to climb stairs for 6 months and difficulty walking across the room for 2 months because of shortness of breath. She had also noticed a progressive hoarseness of several months' duration. She had received a diagnosis of bronchial asthma and congestive heart failure, and had been treated medically for approximately 5 years. She had had no known previous surgical procedures.

Physical examination revealed a large subglottic mass originating from the posterior wall of the larynx. The subglottic air space was significantly narrowed, such that a patent airway passage was not apparent on indirect mirror examination. There were no palpable neck masses. The remainder of the findings on head and neck examination were unremarkable.

RADIOGRAPHIC FINDINGS

Computed tomography of the head and neck with contrast was performed. Multiple enhanced slices of the neck revealed an irregular, heavily calcified 3-cm mass at and below the level of the true vocal cords. The mass contained scattered punctate and ringlike calcific densities. The lesion narrowed the subglottic airway to a 5-mm opening located in the left anterior portion of the trachea. The lesion appeared to be contained by the thyroid cartilage without evidence of direct invasion to the surrounding deep fat planes (see Figure; C,D).

SURGERY

Tracheostomy with subsequent direct laryngoscopy and biopsy were performed with a working diagnosis of laryngeal chondroma. Direct laryngoscopy revealed a large posterior subglottic mass that narrowed the airway and encroached upon the arytenoids. Multiple biopsies were read as nondiagnostic. There was no evidence of inflammation or malignancy.

Later the patient underwent a laryngofissure subglottic mass excision. The mass was noted to be mucosa-covered, indurated, and apparently arising from the posterior wall of the cricoid cartilage and first two tracheal rings. The mass was removed in macroscopic entirety without difficulty or complication. Histopathologic examination of the surgical specimen confirmed the clinical diagnosis of chondroma.

DISCUSSION

Tumors of the larynx are frequently encountered by the head and neck surgeon. The vast majority of these neoplasms are squamous cell carcinomas. Cartilaginous tumors of the larynx comprise only a small number of the nonsquamous neoplasms that affect the larynx. There are about 200 cases of these tumors now recorded in the literature.¹ The location of these tumors in 75% of cases is the endolaryngeal surface of the posterior lamina of the cricoid cartilage. The thyroid, arytenoid, and epiglottic cartilages are next affected, in declining order. The tumors commonly affect men between the ages of 30 and 70. The reported incidence in men is roughly three times that in women.²

The clinical presentation of these tumors is primarily dependent on their location and size. The majority originate in the subglottis and present with stridor, hoarseness, or dyspnea. Tumors in this location eventually lead to some degree of airway obstruction. It is not uncommon for these patients to receive a misdiagnosis of asthma.² Supraglottic tumors may produce hoarseness, dyspnea, dysphagia, odynophagia, or otalgia. Occasionally, extralaryngeal extension will present as a neck mass.³

Cartilaginous tumors are diagnosed on the basis of histopathologic characteristics. Batsakis and Raymond² classify them into four groups: 1) chondrometaplasia, 2) chondroma, 3) chondrosarcoma, and 4) cartilage within otherwise classified lesions. Chondromatous metaplasia of the larynx has been found in up to 2% of human larynx specimens at necropsy.⁴ Hill et al⁴ note that these metaplastic

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Axial computed tomograms. A,B) At true vocal cord level. A) Soft tissue technique with large calcific mass originating in cricoid-arytenoid area producing marked airway compression. B) Bone mode technique of same area. C,D) Ten millimeters below A and B, showing relation of mass to tracheal ring. C) Soft tissue mode. D) Bone mode at same level.

nodules are generally small asymptomatic foci most commonly located in the region of the false cords. They also hypothesize that some chondromas diagnosed in earlier reports may in fact have been chondrometaplastic nodules.

The differentiation between chondromas and chondrosarcomas can be a difficult task. Histologic grading of laryngeal chondrosarcomas is equivalent to the grading scheme used for extralaryngeal chondrosarcomas. Greater than 50% of presenting cartilaginous tumors will be chondrosarcomas, and nearly 50% of these tumors will be low-grade (grade 1) malignancies.¹ These low-grade lesions are easily mistaken for more benign chondromas.

In one of the largest single reports to date, Neel

and Unni⁵ studied 33 patients seen for treatment of cartilaginous tumors of the larynx. Only 2 of these patients had chondromas. The remaining 31 patients had chondrosarcomas. Likewise, two earlier diagnosed cases of chondroma were reclassified as chondrosarcoma after further review. In addition, tumors diagnosed as chondromas have been known to present years later as recurrent low-grade chondrosarcomas.⁶ It is apparent that a diagnosis of chondroma should carry a degree of suspicion, and should be followed for possible future recurrence.

Radiology can be very useful in defining these tumors for surgical procedures. However, diagnosis relies on histopathology. Plain anteroposterior films generally show a discrete mucosally covered soft tissue mass arising from the laryngeal cartilage.

Coarse scattered calcification occurs in 75% of these tumors.⁷ Tomograms and computed tomography can be useful in delineating local anatomy and tumor extension.

In general, benign and low-grade lesions have a favorable prognosis. High-grade lesions are progressive, and up to 10% of patients with these lesions have been shown to die of their tumors.² Metastases are unusual but have been reported. Recurrence rates re-

ported by Neel and Unni⁵ ranged from 21 months to 16 years, with a mean recurrence rate of 6 years.

Treatment for these tumors must be individualized. The malignant potential of the tumor should be ascertained, for this weighs directly on the aggressiveness of the approach taken in management. Whenever possible, conservative treatment is advisable. However, conservative excision has been shown to carry a 65% recurrence rate.²

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THE JERUSALEM SYMPOSIUM ON SURGERY OF THE SKULL BASE AND ADJACENT MIDLINE REGION

The Jerusalem Symposium on Surgery of the Skull Base and Adjacent Midline Region will be held March 21-26, 1993, in Jerusalem, Israel. For further information, contact Dr F. Umansky, The Jerusalem Symposium on Surgery of the Skull Base and Adjacent Midline Region, PO Box 50006, Tel Aviv 61500, Israel; Telephone 972 3 5174571; Telex 341171 KENS IL; Fax 972 3 655674.



AMERICAN DIOPTER AND DECIBEL SOCIETY

The American Diopter and Decibel Society will hold its biennial meeting January 16-23, 1993, at the Westin Camino Real in Puerto Vallarta, Mexico. Abstracts are currently being accepted. For further information, contact Robin L. Wagner, American Diopter and Decibel Society, 3518 Fifth Avenue, Pittsburgh, PA 15213; fax (412) 647-8720, phone (412) 647-2227.

IMAGING CASE STUDY OF THE MONTH

CALCIFICATION OF INTERNAL AUDITORY CANAL TUMORS

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INTRODUCTION

The diagnosis of tumors of the internal auditory canal (IAC) has been greatly simplified by the development of evoked response audiometry, computed tomography (CT), and, more recently, magnetic resonance imaging. The presence of calcification in the IAC is commonly thought to indicate a meningioma.^{1,2} However, calcification can occur in other tumors, including acoustic neuroma. We report three cases of calcified intracanalicular tumors believed to be meningioma, but this diagnosis proved to be accurate in only one case.

MATERIAL AND METHODS

These three cases are presented following a retrospective review of the records of a series of 160 acoustic tumor cases operated on by the senior author (P.A.F.) in the period 1984 to 1990.

CASE REPORTS

Case 1. A 50-year-old male forklift driver presented with a 2-year history of right-sided increasing hearing loss of sensorineural type. A prolonged I-V interval was demonstrated on evoked response

audiometry. A CT scan showed an enlarged IAC. An air CT cisternogram confirmed the presence of a calcified tumor (Fig 1), which was removed by the translabyrinthine approach. It proved to be densely adherent to the facial nerve, which was preserved, but a complete paralysis supervened. Final facial function was classified as House and Brackmann grade 3. Histology showed a schwannoma with extensive Antoni B areas containing hyaline collagen and calcification (Fig 1B).

Case 2. A 26-year-old nursing sister with a long history of total left-sided sensorineural hearing loss presented with a 3-month history of short-lived episodes of vertigo. High-resolution CT demonstrated a calcified destructive mass in the IAC and adjacent petrous apex on the left side (Fig 2). A translabyrinthine approach to the IAC was carried out. The tumor was found to be extremely tough in consistency. It had destroyed the walls of the IAC and was densely adherent to the middle fossa dura. Complete removal would have required facial nerve sacrifice, so subtotal removal was carried out. Two years later, facial nerve function was normal, with no evidence of tumor growth on CT scan. Histologic appearances were of meningioma with nu-

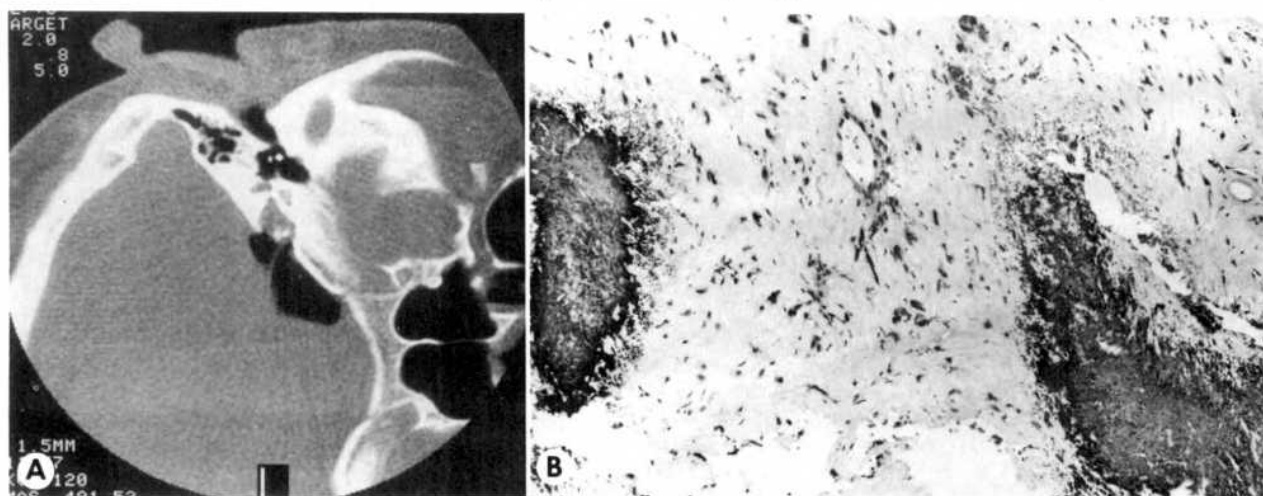
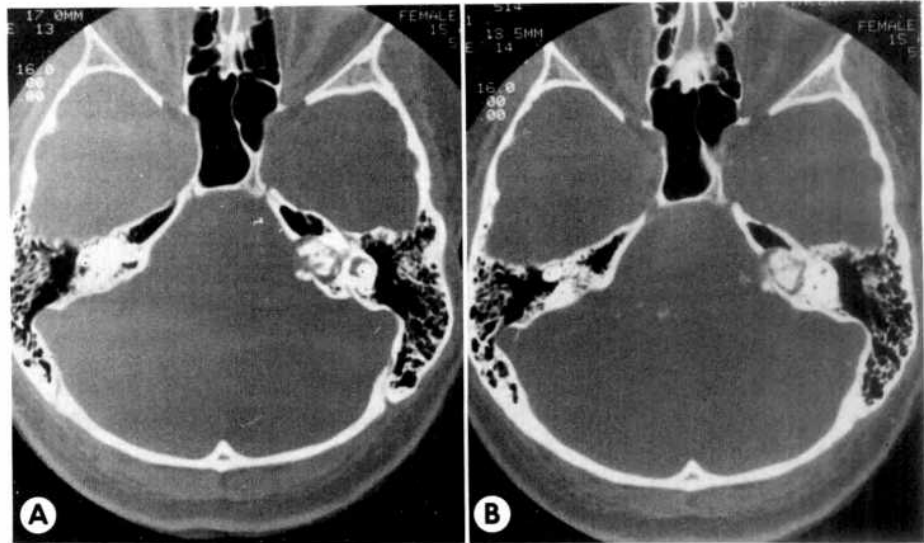


Fig 1. (Case 1) A) Air computed tomography cisternogram demonstrating calcified acoustic neuroma of internal auditory canal. B) Antoni B area of acoustic schwannoma showing hyperchromatic nuclei and collagenous stroma with two large areas of calcification (H & E, original x10).

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Fig 2. (Case 2) Computed tomograms in axial plane, bone window settings. A) Internal auditory canal meningioma at level of horizontal semicircular canal. Extensive calcification is demonstrated. B) Higher cut through superior semicircular canal. Shows dense calcification in internal auditory canal.



merous psammoma bodies.

Case 3. A 38-year-old female hairdresser presented with a flat sensorineural hearing loss of 80 dB on the left side. A high-resolution CT scan showed an intracanalicular enhancing tumor with a calcified or bony mass within. The internal auditory canal was significantly widened (Fig 3A,B). A

translabyrinthine procedure revealed an ovoid, red, fleshy tumor surrounded by a vascular plexus that bled easily. A bony mass lay in the lower aspect of the IAC and the anterior inferior cerebellar artery looped through the tumor. Total removal was carried out with preservation of the facial nerve. Histology showed dilated, thin-walled cavernous vascular spaces and vessels with thick fibrous walls.

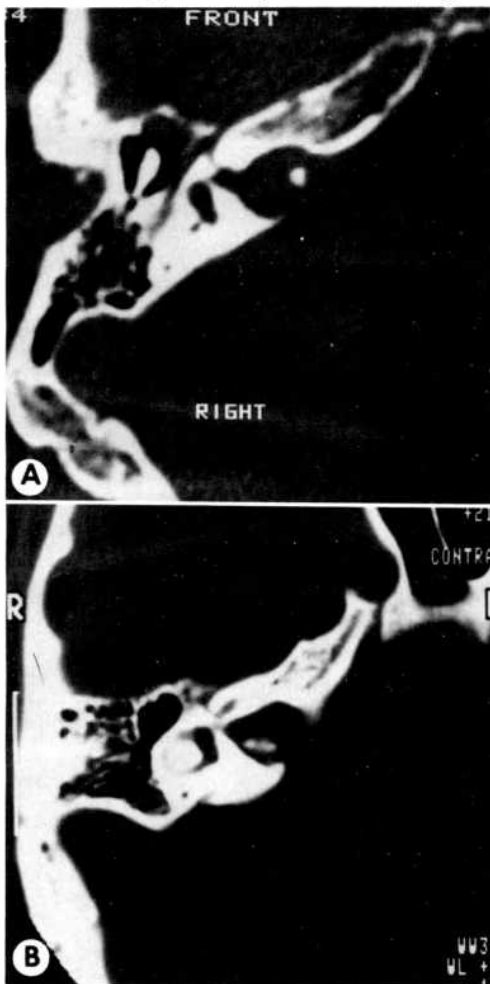
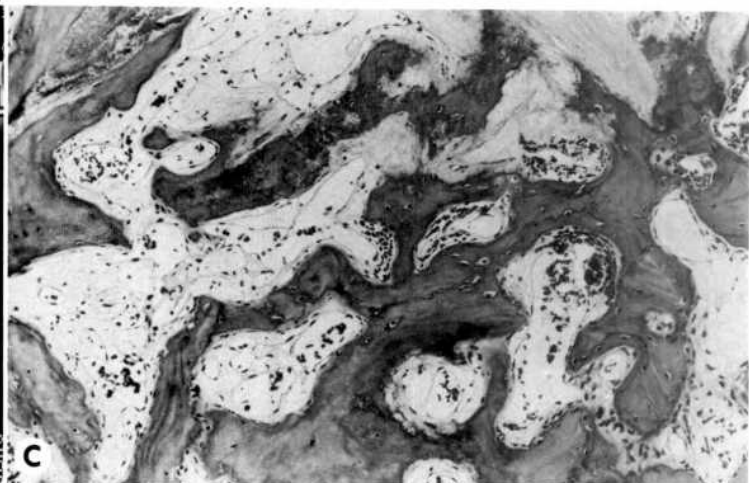


Fig 3. (Case 3) A,B) Computed tomograms through internal auditory canal. A) At level of horizontal segment of facial nerve. Significant widening of canal with intratumoral bone near anterior margin or porus. B) Higher cut at level of geniculate ganglion. Bone is seen in tumor mass near posterior wall of internal auditory canal. C) Cavernous vascular spaces in interstices of "honeycomb" bone (H & E, original x10).



The malformed vessels diffusely involved the endoneurium of the acoustic nerve and were present in the interstices of a "honeycomb" reactive woven and lamellar bone. These were the features of ossifying hemangioma (Fig 3C).

DISCUSSION

Acoustic neuroma is the most common tumor of the cerebellopontine angle and the IAC. Other tumors in this area include meningioma, hemangioma, facial neurilemoma, and cholesteatoma. These tumors present in similar fashion. Preoperative differentiation is usually made on the radiographic features. As the cases described illustrate, these appearances can be misleading.

Calcification with acoustic neuroma may occur as one of the secondary changes in Antoni B areas. Osseous metaplasia is also reported.^{2,3} Characteristic widening of the porus occurs in 77% to 82% of cases.^{2,4} Notably, these features were found not only in the acoustic tumor case (case 1), but also in that of the ossifying hemangioma (case 3).

Psfammomatous meningioma develops numerous particles of calcified material^{1,4} and quite separate areas of bone can be formed.⁵ Meningiomas are generally not concentric with the porus, but when they are confined to the IAC, bone destruction can be extensive (case 2), with facial nerve and labyrinthine invasion.⁶

Intratemporal hemangiomas mainly arise in conjunction with the facial nerve.⁷ These tumors are rare, representing about 0.7% of all tumors in the area, and may mimic an acoustic neuroma,⁸ as occurred in this case. The tumor is composed of thin-walled vascular spaces, and ossification is thought to be due to dystrophic tissue changes. "Honeycomb" bone generally surrounds the tumor,⁷ and bone erosion can be significant, accentuating the radiographic similarity to an acoustic tumor.

Magnetic resonance imaging has continued the revolution in radiographic diagnosis of these tumors. The addition of gadolinium allows detection of small IAC neoplasms. The magnetic resonance imaging signal intensities of meningioma and acoustic neuroma are similar and the major differentiating feature is separation of the tumor and nerve complex.⁹ Pappas et al¹⁰ believe that ossifying hemangioma is consistent with increased signal density on both T1- and T2-weighted images, whereas IAC acoustic neuromas are best seen on T2 signals.

CONCLUSION

Calcification of an IAC tumor is thought to be indicative of meningioma. However, calcification also occurs in acoustic neuroma, ossifying hemangioma, and rarer tumors.

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PATHOLOGY CONSULTATION

CHOANAL AND ANGIOMATOUS POLYPS OF THE SINONASAL TRACT

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Choanal and angiomatous polyps can be distinguished from ordinary sinonasal polyps by either a distinctive clinical presentation (choanal) or the histopathologic appearance (angiomatous). Nearly all choanal polyps arise within paranasal sinuses, with the antrochoanal polyp the most common. The angiomatous polyp is most often a secondary change in a choanal polyp and can be mistaken for vascular neoplasms, eg, angiofibroma.

Choanal polyps can be defined as paranasal sinus polyps that pass through sinus ostia and protrude into the boundary between the nasal cavity and nasopharynx — the choana. The most common choanal polyp is the antrochoanal polyp, sphenchoanal and ethmoidchoanal polyps are rarer.

The antrochoanal polyp originates in the maxillary antrum.¹⁻³ With enlargement it protrudes through the middle meatus into the nasal cavity between the middle turbinate and the lateral wall of the nasal cavity. Posterior extension moves the polyp into the nasopharynx, and a very large antrochoanal polyp can appear as an oropharyngeal mass. A sphenchoanal polyp develops in the sphenoid sinus and passes through the sphenoid ostium into the sphenoid recess, which is in the high nasal cavity above and behind the superior turbinate.⁴ Herniation through the recess places the polyp in the choana. Weissman et al⁴ offer radiographic distinctions between the two choanal polyps. With a sphenchoanal polyp, the polyp is between the nasal septum and the middle turbinate. The middle meatus and the space between the middle turbinate and the lateral wall of the nasal cavity are clear. In contrast, the antrochoanal polyp passes between the middle turbinate and the lateral wall, and the space between the nasal septum and middle turbinate is clear. Whether the ethmoidchoanal polyp arises from the ethmoid air cells or from the nasal cavity is part of the larger debate over the origin of nasal polyps in general.⁵ Anatomic variations of the ethmoid sinus, ill-defined junctions between nasal and ethmoid sinus mucosae, and clefts rather than an ostium make it difficult to precisely identify a site of origin.⁵

ANTRAL-CHOANAL POLYP

It is estimated that between 3% and 6% of all

patients with nasal polyps have the antral-choanal variety.¹ It is usually solitary and is only uncommonly associated with upper respiratory tract allergy. Nasal obstruction is the principal presenting symptom. The ages of patients at the time of treatment are from late childhood or early adolescence to 70 years. The majority of patients are younger than 40 years of age.¹ Sinus radiographs confirm the unilateral antral disease and evince opacity, diffuse cloudiness, mucosal thickening, or polypoid changes. About a quarter of the affected population manifests changes of sinusitis in more than one sinus.

Anterior rhinoscopic examination demonstrates a polypoid mass in the posterior part of the nose. If the polyp is large, it can be found hanging behind the soft palate and in the oropharynx. At times, a stalk of the polyp can be seen in the middle meatus or the ostium of the maxillary sinus. The polyp usually exits the

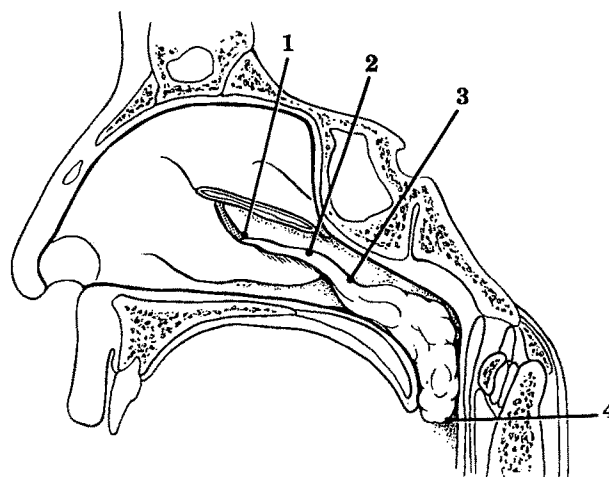


Fig 1. Antrochoanal polyp with four points of vulnerability to vascular compromise capable of leading to formation of angiomatous polyp: at ostial exit (1), at turbinate (2), and in dependent positions (3 and 4).

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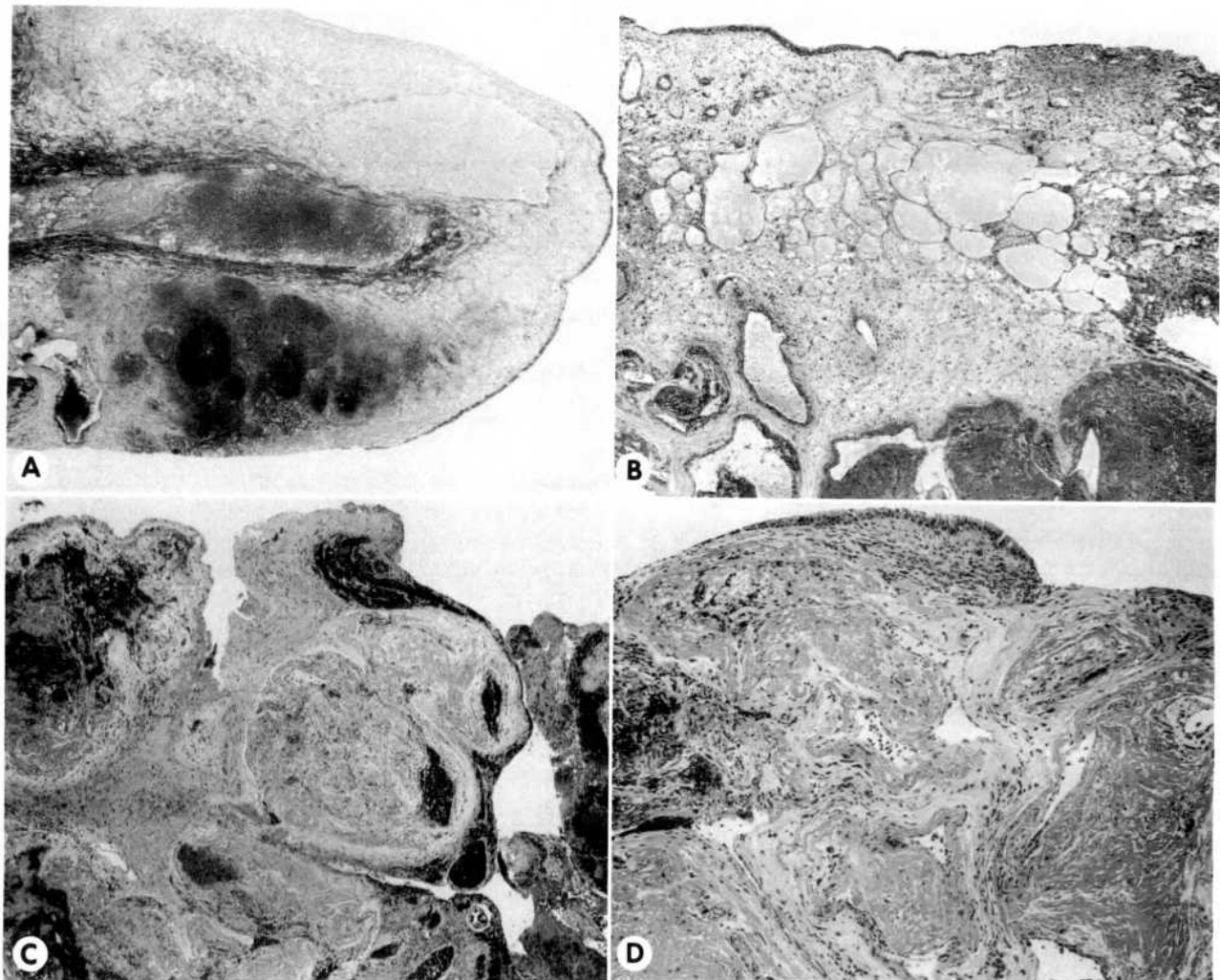


Fig 2. Stages of angiomatous polyp. A) Early angiomatous change in antrochoanal polyp (H & E, original x40). Note dilated and congested vasculature, early hemorrhagic necrosis, and cystic edema of polyp. B) Intermediate stage of development of angiomatous polyp (H & E, original x80). Shows dilated vessels, thrombosis, and beginning neovascularization. C) Late-stage angiomatous polyp (H & E, original x40). There is irregular proliferation of vessels with continuing thrombus formation and fibrosis. D) Higher magnification of late-stage angiomatous polyp (H & E, original x120).

maxillary sinus through the natural maxillary ostium, less often via an accessory ostium or through a surgical defect.^{1,2} The natural ostium often appears enlarged.

The antral part of the polyp can be cystic or polypoid, with its origin often obscured by a generalized thickening of the mucosa. The medial antral wall, region of the inner maxillary ostium, posterior nasal fontanelle, and/or maxilloethmoid angle of the maxillary sinus have all been described as points of origin by the tracing back of the pedicle joining the "dumb-bell-shaped" polyp.²

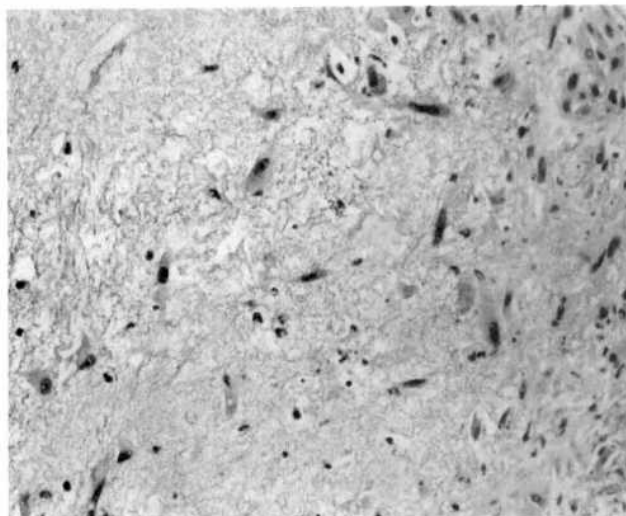
Absent the characteristic gross findings, it is not possible to diagnose an antrochoanal polyp solely on histopathologic findings. Paucity of eosinophils and mucous glands is not unique to this type of sinonasal polyp.

Treatment consists of removal of the antral as well as extra-antral parts of the polyp. Failure to do so results in a nearly 25% recurrence or persistence rate.¹ Kamel³ has outlined the various surgical approaches.

ANGIOMATOUS POLYP

Choanal polyps are particularly susceptible to vascular compromise, eg, origin within a confined space, passage through constrictive ostia, and dependent positions in the nasal cavity, choana, or nasopharynx. Figure 1 depicts four extra-antral sites of vulnerability for the antrochoanal polyp. Occlusion or compression of feeder vessels in the polyp sets up the following sequence: 1) dilation and stasis of feeder vessels, 2) edema, 3) infarct, 4) neovascularization, 5) repeat occlusion, and 6) infarct. The end result, depending on the stage of development at the time of removal, is

Fig 3. "Pseudosarcomatous" fibrohistiocytes in edematous stroma of angiomatous polyp (H & E, original x160).



either total necrosis or, more often, an angiomatous polyp (Fig 2).

Little can be found in the literature about the angiomatous polyp.^{6,7} It is not a variant only of choanal polyps, but is most often a derivative of that

form of polyp. It is not neoplastic, but can be radiologically and pathologically confused with angiofibroma or other vascular neoplasms.⁶ We have also found that a pseudosarcomatous stromal cell change (Fig 3) often accompanies the angiomatous polyp.^{8,9}

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BOOK REVIEWS

Otolaryngology

Michael M. Paparella, Donald A. Shumrick, Jack L. Gluckman, and William L. Meyerhoff, eds. 3rd ed. Vols 1-4. Hard cover, illustrated, indexed, 1991. WB Saunders, New York, NY, \$450.

A fourth volume has been added to the long-awaited third edition of this excellent general overview of otolaryngology. Those familiar with the 1980 second edition will appreciate that it took the intervening years to revise it and add to it the vast amount of information this third edition provides. The most noteworthy innovation is the section on surgical techniques, which includes more detailed and exacting descriptions and could be used as a surgical atlas on certain topics.

Each of the four volumes was designed to cover a category in otolaryngology. A few categories do not follow such a pattern neatly, however, and organizational problems arise that interrupt the otherwise smooth transition of topics and may confuse the reader. For example, "Otolaryngologic Manifestations of Systemic Diseases and Pain," which appears in the basic science volume, would better complement the plastic surgery volume, in which other general clinical topics are addressed. Also, cleft lip and cleft palate surgery is addressed in the head and neck volume, while most would agree that it falls more naturally into the plastic surgery section.

The isolated instances of seemingly misplaced sections generally do not detract from the quality of the information they provide, and overall the volumes are remarkably well edited and well organized. Each volume is well referenced for the reader who desires to pursue an area in greater detail.

Those who admired the two previous editions of this work will not be surprised that the editors have produced a concentrated, definitive reference for residents and practitioners in otolaryngology. Although some of the information contained in these volumes may be outdated and some opinions may have changed, these four volumes represent the most accurate information presently available in book form. Without hesitation, the reviewers recommend this superb edition to all practitioners and those in training in the field of otolaryngology.

Vol 1. Basic Science and Related Principles

The nine sections of this volume include 45 chapters in which embryology, anatomy, physiology, histology, pathology, biochemistry, microbiology, pharmacology, general medical and surgical principles, and otolaryngic manifestations of systemic disease are discussed.

The otolaryngologist who seeks information regarding immunology only to be frustrated by esoteric discussions will welcome the chapter "Immunobiology." Because of the fast pace of research being done in this area and the time required to bring a book of this nature to press, some of the information is slightly dated. For example, some of the thoughts about interferon and complement have changed since its publication. However, to the practicing otolaryngologist, such problems may be of little importance, and this concise chapter furnishes a readable summary of reasonably current concepts.

This first volume gives illuminating, pertinent, and well-written coverage of a broad area of otolaryngology. Unfortunately, those standards are not met by the section on acquired immunodeficiency syndrome (AIDS), which consists of one and a half pages in which only a review of the practical medical concerns and regional manifestations is presented. Information should be the crux of any discussion of a disease that poses as great a threat as AIDS. The effects of AIDS on hearing are not adequately addressed. Statistics on conductive and sensorineural hearing loss would have been welcome, as would a discussion of how and when hearing loss in an AIDS patient should be treated. A discussion of the immunobiologic theory of increased cancer risk in the AIDS patient would also be pertinent.

The strongest point by far in this section is the emphasis on basic principles. These principles form the very foundation of scientific research and growth, and the editors continually remind us that this fundamental knowledge is crucial to mastering the specialty. The editors have successfully and succinctly provided a fairly comprehensive review of the basic subjects necessary to understanding otolaryngology.

Vol 2. Otology and Neuro-otology

This three-section volume consists of 55 chapters in which diagnosis of ear disorders, audiology, and ear diseases are discussed. A discussion of technological advances that have improved diagnosis and treatment and a description of refined surgical techniques add new information and depth to this third edition.

The chapters on physical examination of the ear are well written and cover the basics of the otologic examination. Although vestibular testing is adequately presented in discussions of modern, computerized procedures, it would have been enhanced by the inclusion of procedures that can be performed in the examination chair (Dix-Hallpike, simple calorics, Frenzel glasses, etc.). An awareness of these could produce a quicker presumptive diagnosis and be of value to the clinician and patient when the more sophisticated procedures are not readily available.

The role of audiology in diagnosing and managing ear diseases is well presented. Most readers will no doubt be pleased that the sections on electrical response audiometry and hearing aids have not been overburdened with engineering details that can be found in other sources. All otolaryngologists should be familiar with assistive devices in order to best advise their hearing-impaired patients, and up-to-date information is given in the chapter dealing with such aids. Also presented is the role of the otolaryngologist in monitoring acoustic safety in accordance with the standards of the Occupational Safety and Health Administration.

Chapter 32, "Mastoidectomy and Tympanoplasty," is an excellent example of the quality of writing found throughout these volumes. While it describes one particular technique for each type of surgery, a greater portion of this text is devoted to emphasizing principles of otologic surgery, which is the essential purpose of a book of this type. The section on radical mastoidectomy, in which the indications, objectives, and options in incisions are discussed, is but one example of achievement of this goal. It is a tribute to the philosophy and experience of the editors that this entire volume is ripe with such germane information.

"Meniere's Disease and Other Labyrinthine Disorders" (Chapter 49) is primarily consumed by all aspects of Meniere's disease, including practical clinical tips regarding patient care gleaned from the author's vast experience. Other labyrinthine disorders are also addressed, however briefly. Perilymphatic fistula is discussed in an abbreviated fashion. The author does not clearly state an opinion as to whether all Meniere's patients should undergo exploration for this condition. All in all, this chapter is an excellent overview (especially of endolymphatic hydrops) that benefits from the author's extensive collection of temporal bone specimens and reflects his exhaustive knowledge of temporal bone pathophysiology.

The remaining chapters in this volume are equally well written and only because of space are not detailed here. Within this volume, however, is one of the more complete guides to temporal bone dissection. The illustrations and text are of such quality that this could be used as a dissection guide by a first-year resident. This by no means indicates that this section is simplistic or basic, for there is much to be gleaned from this chapter for the experienced otologist, and it is well worth the time to review.

Vol 3. Head and Neck

The introduction to this volume is written by the quintessential head and neck surgeon, John Conley. He powerfully but concisely sums up the goals of head and neck surgery as it should be prac-

ticed in the coming decade while reviewing the historical background of the leadership role otolaryngology has assumed in this regional subspecialty.

More than just the usual coverage of head and neck neoplasms is included. Functional endoscopic surgery, taste and smell disorders, professional voice, congenital abnormalities, thyroid and parathyroid disease, and cancer therapy are also covered. Facial plastic surgery, which appeared in this section in earlier editions of this book, now is included in a separate volume. This change enabled the editors to present new topics and expand on conditions of the head and neck in an organized fashion. From the initial chapter, the changes and developments in otolaryngology are noted. The section on examination of the head and neck, based on time-honored principles, has been modified to reflect technological advances in fiberoptic lighting and scopes that have improved clinical assessment. Mention is made of video and photographic advances that make documentation more accurate, as well as protect the physician in this day of medical litigation.

The cleft lip and cleft palate section is one of the most well written we have seen in any text. The surgical anatomy and repair of these abnormalities is succinctly described. The editors deserve praise not only for their comprehensive review of the facial clefts, but their inclusion of the ever-increasing role of prosthodontics in the rehabilitation of this congenital defect. The illustrations are clearly and impeccably reproduced and add a great deal to the already comprehensive text.

Disorders of the oral cavity, pharynx, and larynx are well covered in this edition and in fact make up the brunt of the third volume. The quality of the writing, as well as the depth of information, is consistent with the other volumes. All chapters contain the most up-to-date information. Most noteworthy is the addition in the laryngeal chapters of the care of the professional voice. This is an area certainly within the realm of otolaryngology, but it has been given low priority in favor of large surgical procedures. Topics like this are assuming an important role in today's clinical practice and deserve consideration in a text of this nature.

The remainder of volume 3 deals with neoplasms of the head and neck, including head and neck cancer. As one would expect from the reputation of the editors, these chapters contain years of experience in the field. For both benign and malignant lesions, this could be used as a definitive reference that is certainly more than adequate. In fact, the description of surgical technique is better than that of any other general otolaryngology reference in print at this time. The sections on head and neck reconstruction have been updated to include microsurgery, while retaining the tried and true techniques of musculocutaneous flaps.

Further improvements in the chapters on endoscopy and thyroid and parathyroid glands would make other specialties envious because of the excellent review of the material. Well-drawn illustrations and tables accompany the text, providing easily retained information.

Vol 4. Plastic and Reconstructive Surgery and Interrelated Disciplines

This well-organized and beautifully illustrated synopsis of head and neck plastic surgery clearly defines the role of the otolaryngologist in a field that encompasses many different medical specialties. The second of the two sections (32 chapters) is noteworthy because it is not related to plastic surgery, but to disciplines closely related to otolaryngology. These areas include anesthesia, ophthalmology, neurology, and radiology.

The rapid growth of neuro-otology over the last three decades has resulted in more otolaryngologists becoming involved in the neurosurgical procedures, especially for posterior fossa lesions. Chapter 23 provides an extremely timely introduction to these overlapping areas. While the coverage is not comprehensive, it is most desirable and a progressive step toward improved patient care and procedure safety.

Also exceptionally relevant, because it dovetails so nicely with the growth in endoscopic sinus surgery, is the chapter devoted exclusively to exophthalmos. Although that topic has appeared

more recently in the oculoplastics literature, otolaryngologists also play a role because of the related anatomy.

Two topics in this volume that are especially pertinent are 1) photography and 2) psychology of the patient with hearing loss. Photography of the head and neck is desirable in patient follow-up and a prominent need in medicolegal issues. Modern technology has made photographic configurations available for any office or surgery environment, and the guidelines to better photographs presented in this section are welcomed.

Most of the chapters on plastic surgery are well written and easily read. The accompanying illustrations are good enough that this can be considered an atlas on most topics. All areas are covered, from soft tissue techniques to major reconstructions of the head and neck. Included is the topic of microvascular tissue transfer. While this is not a technique to be used by all otolaryngologists, everyone should be familiar with the indications and capabilities in order to better serve the patient. The section on orthognathic surgery is illustrative, but less inclusive than other sections in this book. The surgical technique for maxillary and mandibular osteotomies is useful for the otolaryngology resident, but this should by no means be the only source consulted for information on these topics. In a similar vein, the chapter on facial fractures gives background and basic information, but is somewhat dated in its failure to mention some of the current concepts on facial fractures. Plating of mandibular and maxillary fractures is only mentioned and not given the consideration it deserves. While those otolaryngologists with a great deal of experience in this field might agree that too much emphasis has been placed on opening facial fractures, rather than treating them conservatively, the fact remains that plating, as well as bone grafting, is an integral part of treatment plans. As such, this topic should be explored. The surgical techniques are barely covered. Overall, this volume will probably be the focus of the residents who purchase this set. With the exception of the chapters on orthognathic surgery and facial fracture repair, this is a well-written volume.

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Atlas of Allergies

Philip Fireman and Raymond G. Slavin, eds. Hard cover, illustrated, indexed, 243 pages, 1991. JB Lippincott, Philadelphia, Pa, \$95.

The introduction to this book is a comprehensive review of immunology as it relates to allergic mechanisms. It contains 1) a good review of leukopoiesis and lymphoid cell maturation, 2) an up-to-date review of lymphoid and myeloid lineage-specific markers and cluster designation nomenclature, 3) a contemporary review of T-cell receptor structures and function, 4) a fairly extensive review of interleukins 1 to 6 and their role in immune regulation (the recently described interleukins 7 to 11 and interleukin 12 are not covered), 5) an easy-to-read review of relevant cytokines such as colony-stimulating factors, interferons, and even tumor necrosis factor, and 6) a brief summary of human immunoglobulin subclasses (error on page 1.16) and their interaction with subclass-specific Fc receptors.

The immunology section is concluded with information explaining the mechanisms involved in type I, II, III, and IV hypersensitivity reactions and how they are involved in allergy. The remainder of the text describes how allergic reactions impact on various medical specialties such as dermatology, otolaryngology, and others.

In addition to providing a good review of basic mechanisms, the book contains a series of excellent photographs on a level that would be useful to both professionals and parents interested in understanding allergic reactions and the rationale behind skin, inhalant, and oral testing.

Our only criticism of this text is that more detail could have been provided to explain the rationale and mechanisms of allergy

testing, treatment, and desensitization. Also, although the possible severity of some allergies is demonstrated by examples of extreme reactions, examples of less severe reactions would have been more useful in providing early detection guidelines.

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Diseases of the Nose, Throat, Ear, Head and Neck

John Jacob Ballenger, editor. 14th ed. Hard cover, illustrated, indexed, 1,376 pages, 1991. Lea & Febiger, Philadelphia, Pa.

This one-volume book touches on all aspects of otolaryngology and head and neck surgery. Its consequent size yields both advantages and disadvantages. The major advantage is that it is a one-touch reference. The disadvantage is the sheer weight of the book, which requires a special table for storage. This is the 14th edition of the text, the first of which was printed in 1908. All editions have been edited by a member of the Ballenger family, establishing an 83-year tradition of service to otolaryngology that deserves high praise. It is hoped that this tradition will continue.

This text, which is divided into six sections, has a great many strong points, the first of which is scope. The chapters on squamous cell carcinoma of the head and neck are particularly strong. Although the authors of these chapters present philosophically conservative approaches, they do not rehash old dictums in head and neck surgery, but discuss new treatment options and include the most current research ideas. Moreover, the chapters are very easily read and are complemented by well-organized tables.

Other sections of this book also deserve accolades. The section on sinus endoscopy is well written and includes a short but complete description of surgical technique, as well as the potential hazards in this relatively new field. Equally as well written is the part on surgical correction of facial deformities, which describes in detail the important points of rhinoplasty.

The section on imaging of the head and neck is worth special mention. It reduces a very complex and highly technical subject to simple terms, so that one not so well versed in radiology can better understand some of the biophysical principles involved. Without ignoring the value of other radiographic studies, this chapter emphasizes magnetic resonance imaging and computed tomography, providing very good pictures to accompany the text.

The section on audiology and ear disease is fairly complete and particularly well written, especially for the limited space devoted to it. Historical perspectives on anatomy and physiology of the ear are extensively reviewed and easily understood. This portion of the book could easily serve as a quick reference for even the most experienced otologist. The discussion on methods of ossicular reconstruction is complete, albeit brief. Rather than espousing one particular type of prosthesis or reconstruction, the author provides an overview of options, depending on the situation. The role of homografts in reconstruction is mentioned. Because of the medicolegal ramifications in our society today, the use of homologous materials must be weighed carefully; we question the preservation technique described by the author. The portion on skull base surgery, while informative, is not as complete as the otologic section. However, the discussion of vestibular diseases is worth the time spent reading.

The discussion presented in the bronchoesophagology section is well written and fairly comprehensive. The chapter takes care to include descriptions of those procedures that overlap into the field of otolaryngology, such as gastroscopy and duodenoscopy. The bronchoscopy section reviews technique and necessary equipment extremely well.

There are few criticisms to be found for this book. If one were pressed, the main criticism would be the lack of detail in some of the chapters. Detail is not found in some areas of anatomy (in particular some of the finer detail of the larynx, including well-

known eponyms), some surgical techniques (especially in facial fracture repairs), and some physiology. For example, in nasal physiology some of the basic science discussion lacks the detail that is found in the more recent literature. This deficit must be viewed from the standpoint that this is only a one-volume text and therefore not meant to be all-encompassing.

Dr Ballenger accomplished what he stated in the preface to be his intent: to provide a basis for the practice of clinical otolaryngology. He has provided a book that is an excellent general reference of the field in a single volume. If further detail is required, all of the chapters are well referenced with contemporary sources. The book is well-suited for both the general otolaryngologist and the nonotolaryngologist who seeks a good shelf reference. Its size and topic coverage produce a useful, well-written book that is highly recommended.

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Rhinitis

Guy A. Settipane, ed. 2nd edition. Hard cover, illustrated, indexed, 344 pages, 1991. OceanSide Publications, Inc., Providence, RI, \$68.

This is the most comprehensive text available about a very complex and often misunderstood subject. This second edition is expanded by the number of chapters and authors, making it more comprehensive than the first edition.

Chapter 35 is weak. It discusses the comparisons of the various methods of skin testing with specific allergenic extracts. The authors do discuss historical perspectives; however, they fail to mention that the members of the Council on Scientific Affairs of the American Medical Association in 1987 stated that "scratch tests are less reproducible than prick and puncture tests and are no longer recommended" (Allergy Panel. *In vivo* diagnostic testing and immunotherapy for allergy. *JAMA* 1987;258:1363-7). In addition, the intradermal technique of serial end-point titration was not dealt with historically or in its current perspective. Serial end-point titration, according to the members of the AMA Council on Scientific Affairs, is considered an acceptable method of testing.

With the exception of Chapter 35 the book is an excellent reference source for allergists, otolaryngologists, and rhinologists. It reads well, the graphic data are clear, and it conveys a wealth of knowledge covering most aspects of rhinitis.

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Surgery of the Thyroid and Parathyroid Glands

Blake Cady and Ricardo L. Rossi. Hard cover, illustrated, indexed, 348 pages, 1991. WB Saunders, Philadelphia, Pa, \$75.

This is an excellent textbook. The text is divided into 31 chapters, with the first 10 devoted to histopathology, physiology, imaging, physical examination, and fine needle aspiration. The next 11 chapters are concerned with thyroid disease and its diagnosis and management. Each chapter is well written and balanced, with line drawings, radiographic studies when applicable, and clinical and histopathologic photographs. Clinical correlation is emphasized, surgical technique is described, and special commentary sections in 8 of the chapters provide further insight into the diagnosis and treatment of these diseases.

Surgery of the Thyroid and Parathyroid Glands by Cady and Rossi is an excellent addition to the library of any head and neck surgeon. Otolaryngology residents would benefit from this text as well.

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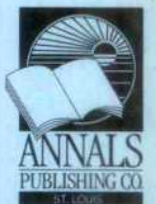
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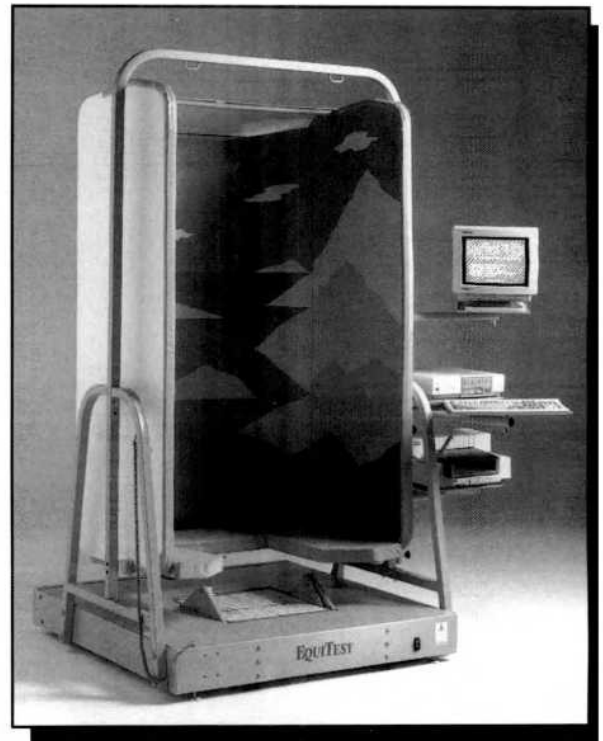
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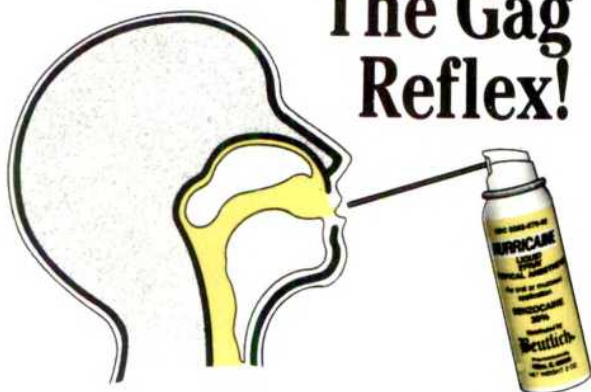
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Zoom endoscopic electromyography of the larynx, as introduced in 1979, has contributed greatly to the diagnosis of lower cranial nerve palsies, but in the early stage of a vagus nerve disorder one cannot investigate the nerve conduction from the brain stem to the laryngeal muscles with electrical stimulation. As with the early diagnosis of facial nerve palsies, up to now the intracranial part of the motoric brain nerves could not be stimulated directly. With a new magnetic coil device (Novametrix, Magstim 200) this intracranial stimulation is easily possible in the awake patient with painless magnetic stimuli that induce a muscle action potential into the laryngeal muscles. Hence, an immediate diagnosis is possible. Two coils with mean diameters of 8.5 or 3 cm were used. The stimulator delivered current pulses of peak amplitude up to 5,000 A with rise times of 140 microseconds and 65 microseconds, respectively, that generated peak fields of up to 2 T. In a healthy population, cisternal stimulation of the vagus nerve leads to a muscular response in the vocal muscle after 4 to 6.6 milliseconds (mean 5 milliseconds). Cortical stimulation leads to such a response after 9.5 to 12 milliseconds. Potentials in healthy individuals have been shown to be very uniform. Stimulation in recurrent nerve palsies may show prolongation of these latencies up to 30 milliseconds. The method is limited by the fact that complete neural blocks cannot be overcome by proximal stimulation. We have applied magnetic stimulation to 190 patients with different disorders of the vagus nerve. It allows a differential diagnosis of palsies immediately after their onset, and is thus the first method to make such an early investigation possible.

KEY WORDS — laryngeal electromyography, lower cranial nerves, magnetic stimulation, neuromyography, palsy, recurrent laryngeal nerve, vagus nerve.

INTRODUCTION

Vital dysfunctions of breathing and swallowing, dysphonia, and speech disorders show up as symptoms of neuromuscular diseases of the larynx. In order to function properly, the larynx must achieve near-perfect synchronization of its intricate sensory and motor capabilities. In addition, the pharyngeal muscles and even the neck and thoracic muscles are often involved. A variety of neurologic diseases appear with central or peripheral impairment of coordination of these muscles or complete loss of function, causing pathologic movements or a direct mechanical failure of the caudal cranial nerves and their coordinated muscles.

Alterations in voice, globus hystericus, and dysphagia are early or even the only symptoms of neurologic or neuromuscular diseases of the oropharyngeal and laryngeal structures. Saccadic movements of the vocal cords causing a poor or unstable voice may be the first sign of multiple sclerosis. Bulbar paralysis, Parkinson's disease, brain tumors, and multiple sclerosis often show up as diminished amplitude and disturbance of vocal cord vibration during stroboscopy

or as paradoxical movements of the vocal cords.

Another early symptom of these diseases may be a deglutition disturbance that later results in increased muscle tension, loss of coordination, or incongruity of function leading to disturbances of swallowing or aspiration.

We need diagnostic tools to determine the site and degree of the neuromuscular lesion, and classification of the type of nerve damage according to Seddon.¹ Diagnostic tools such as electromyography (EMG) and neuromyography (NMG) are necessary to solve this problem, but are difficult to use in the hidden muscles of the larynx and pharynx.

The zoom endoscopic application of tiny copper wire electrodes into the laryngeal and pharyngeal muscles of the awake patient as introduced by Thumfart et al²⁻⁴ permits EMG and NMG of the laryngeal and pharyngeal structures with voluntary movements by the patient as well as electrical stimulation of the vagus nerve in the neck. This should result in an early differentiation of a vagus nerve palsy into degenerative causes such as axonotmesis or neurotmesis and

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Presented at the meeting of the American Laryngological Association, Waikoloa, Hawaii, May 4-5, 1991.

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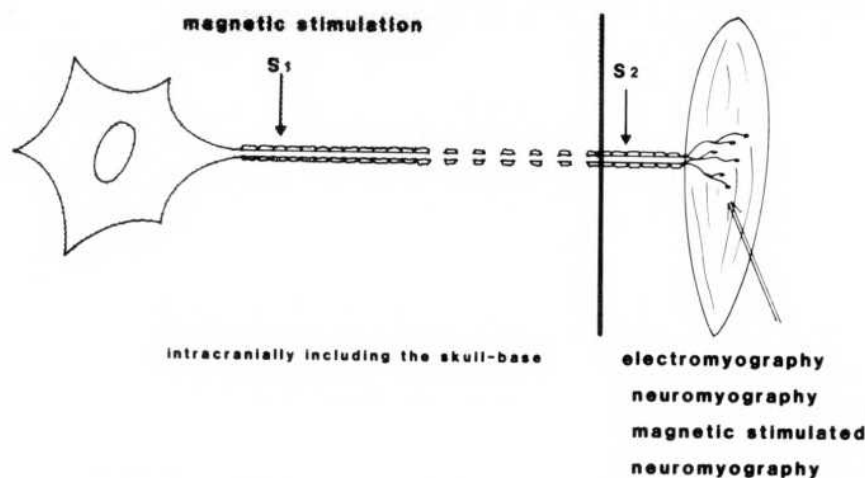


Fig 1. Schematic drawing of magnetic stimulation of lower cranial nerves in comparison to conventional electrodiagnostic methods. S1 — stimulation site 1 (intracranial), S2 — stimulation site 2 (extracranial).

causes with a better prognosis, such as neurapraxia with demyelination without axon degeneration. In neurologic diagnosis with NMG, direct supramaximal stimulation of the nerve proximal and distal to the site of its lesion shows changes in the latency configuration of the muscle response. The proximal stimulation of motoric brain nerves has been a specific problem of cranial nerve diagnosis, since the area of damage of the cranial nerves mainly lies intracranially or at the skull base and is not accessible for electrical stimulation. This problem now seems to have been solved for routine diagnosis by magnetic stimulation, first described by Barker et al⁵⁻⁷ in 1985. It allows an examination of the lower cranial nerves in the awake patient by stimulation of the proximal nerve endings across the lesion.

MATERIALS AND METHODS

Magnetic stimulation (Novametrix, Magstim 200) permits an examination of the facial nerve^{8,9} and

other lower cranial nerves in the conscious patient in routine diagnosis by stimulation of the proximal nerve ending across the lesion (Fig 1).

We used two coils with mean diameters of 8.5 or 3 cm consisting of 20 windings that delivered current pulses of peak amplitude up to 5,000 A with rise times of 140 microseconds (μ s) and 65 μ s, which generated peak fields of up to 2 T (Fig 2).

The magnetic impulse, because of its rapidly changing intensity, induces an electrical current in the surrounding tissue and liquids that reaches approximately 25 mA/cm² with its current density in an annulus underneath the coil, and a flow of direction contrary to the coil current flow.

Depending on the position of the coil, the flow of current stimulates a nerve activity potential underneath the coil and leads to nerve stimulation and a muscular response.

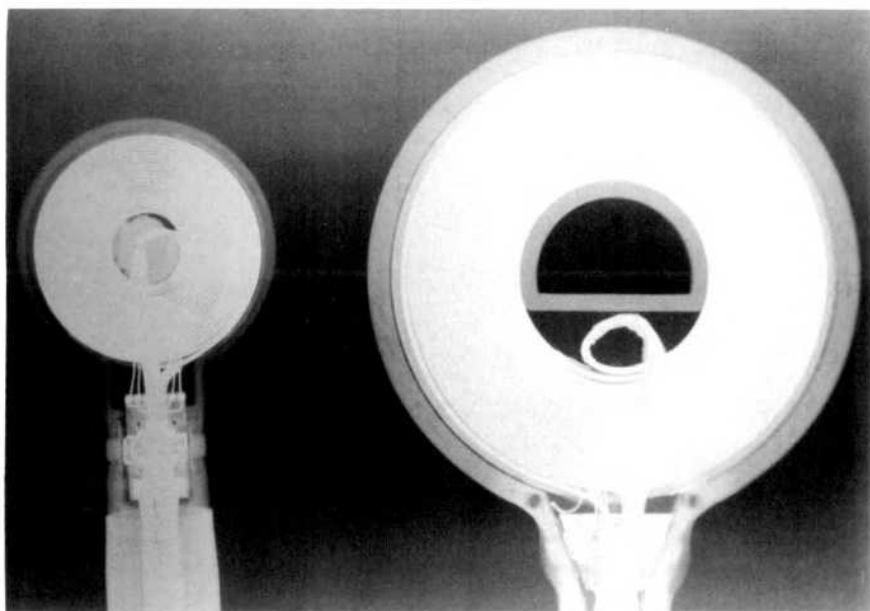


Fig 2. Coil geometries of different types in radiography technique.

TABLE 1. METHODS

Endolaryngeal and/or transcutaneous electrode application
Bipolar hooked-wire or needle electrodes in position
Spontaneous and voluntary electromyography
Electrically stimulated neuromyography and reflex myography
Magnetically stimulated neuromyography
Cortical
Cisternal
Peripheral

Time-varying magnetic fields pass through high-resistance structures such as the skin and skull without attenuation and induce electrical current flow proportional to the tissue conductivity. Thus, magnetic stimulation leads to a depolarization of the deep-seated neural structures that is completely painless, in contrast to the supramaximal stimulation in NMG or reflex myography. Nerve stimulation of the intracranial portion of the lower cranial nerves can be performed from the contralateral cortex, the ipsilateral vertex, and the ipsilateral skull base area for cisternal stimulation, as well as along the neck for vagus nerve stimulation.

The bipolar hooked wire electrodes for EMG recording are placed transorally after surface spray anesthesia in the awake patient under zoom endoscopic control.

The special electrode-holding forceps is immediately withdrawn after application of the electrodes to the vocal muscle or the posterior cricoarytenoid muscle. These electrodes are also suitable for recording of the palatal muscles, lingual muscles, and cricopharyngeal muscle. In less cooperative patients, bipolar needle electrodes are applied transcutaneously or inserted transorally under general anesthesia for successive measurements. A Tönnies TESI II two-channel electromyograph with a programmable recording system was used for recording of spontaneous and voluntary activity in the target muscles of the lower cranial nerves with an amplifier band pass of 20 Hz to 10 kHz.

Standard NMG was performed with a constant current of up to 20 mA at 200- μ s duration, and at a rate of 2 Hz, with bipolar surface electrodes. A similar technique was used for stimulation of the upper laryngeal nerve in order to stimulate reflex myographic potentials. The NMG analysis time was 5 milliseconds (ms) per unit with a 1-ms delay of the stimulus. A Novamatrix Magstim 200 stimulator generated a brief magnetic field with approximately 2 T and maximal output after 140 μ s underneath the coil (center diameter 8.5 or 3 cm, depending on the coil type). Cortical as well as cisternal stimulation

TABLE 2. SUBJECTS (N = 190)

Healthy subjects	52
Patients	138
Traumatic (iatrogenic) recurrent nerve palsies	60
Idiopathic recurrent nerve palsies	35
Spasmodic dysphonia	7
Guillain-Barré polyneuritis	7
Multiple sclerosis	5
Parkinson's disease	3
Apoplexy	11
Congenital laryngeal palsies	10

was employed with a stimulus intensity of 70% of the maximal output. The amplitude units are 1 mV per unit for EMG and 500 μ V per unit for magnetically stimulated NMG.

With the electrodes held in position, magnetically stimulated NMG was performed after EMG recording (Table 1). For cortical stimulation at the vertex, the coil center (center diameter 8.5 cm) is positioned 4 cm below the vertex in relation to the jugular foramen. The coil is then moved down to approximately 2 cm behind and 6 cm above the external auditory canal for stimulation of the nerves at their cisternal part. Direct peripheral stimulation of the vagus nerve was done with the smaller coil (center diameter 3 cm). Latency, peak-to-peak amplitude, response duration, and peak integral were determined with the use of cursors. All responses were

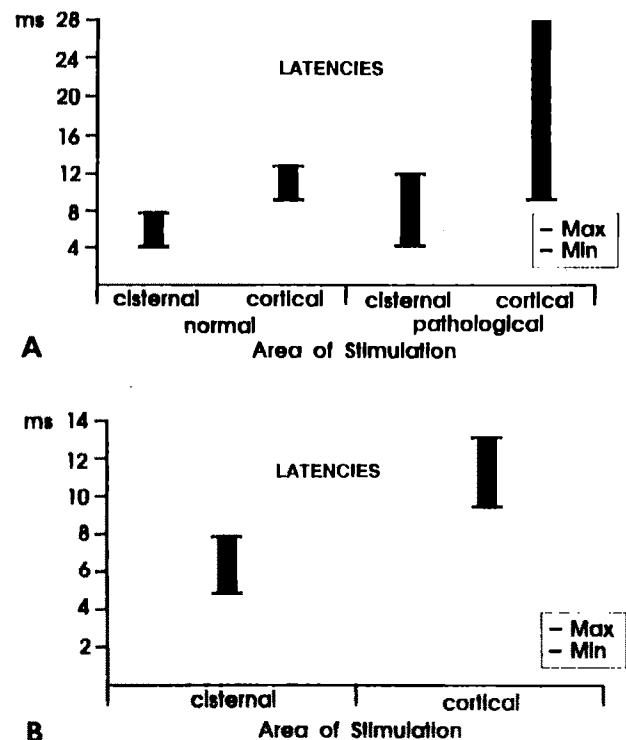


Fig 3. Mean values of latencies for magnetically stimulated neuromyography. A) Cranial nerves. B) Recurrent laryngeal nerve.

Magnetic Stimulated Neuromyography

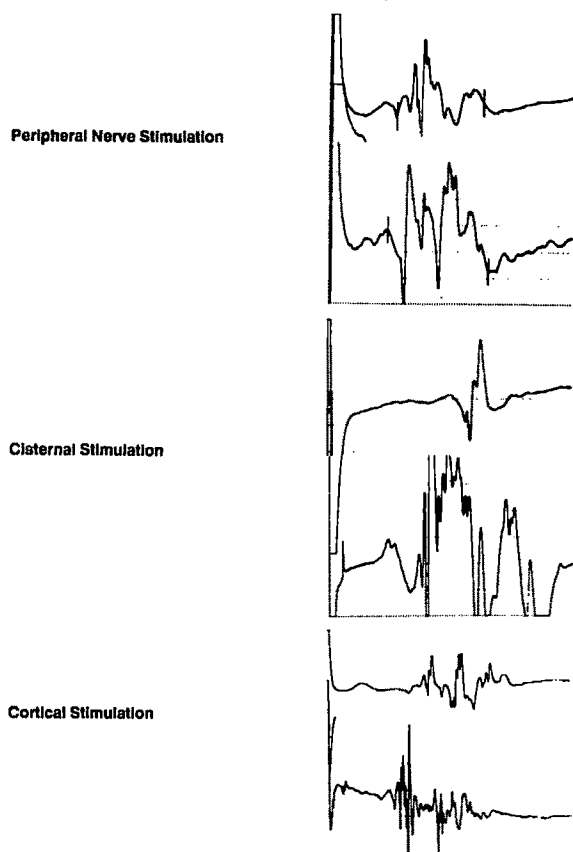


Fig 4. Magnetically stimulated neuromyograms following peripheral, cisternal, and cortical stimulation of motor action potential in vocal muscle ($500 \mu\text{V}$ per unit; 1 to 2 ms per unit; 2 to 5 ms per unit, respectively).

recorded at least twice in order to observe reproducibility or were analyzed by an averager. (No averaging was necessary if there was a clear response after two samples.) The values for healthy and disturbed nerve systems were compared, as well as the results of electrical and magnetic stimulation.

The subjects were 52 healthy subjects with larynges with intact innervation, as well as 138 patients with a variety of lower cranial nerve diseases, including congenital laryngeal palsy in infants (Table 2).

RESULTS

In healthy subjects, EMG of the vocal muscles showed a typical voluntary activity starting 300 ms before the onset of voice and during voice production. Spontaneous activity, on the other hand, was found in degenerative palsies without voluntary activity, as previously reported. Electrically stimulated NMG induced a muscle action potential (MAP) after a latency of 6 to 8 ms. Electrically stimulated reflex myography of the superior laryngeal nerve elicited a reflex MAP after 22 to 26 ms, depending on the side, according to the different lengths of the vagus and



Fig 5. Cortical magnetically stimulated neuromyogram in case of neurapraxia ($500 \mu\text{V}$ per unit; 5 ms per unit).

recurrent laryngeal nerves.

Cortical magnetic stimulation in a healthy population led to a muscle response after 9.5 to 12 ms (SD 1.4; mean 10.8 ms). Cisternal stimulation of the vagus nerve caused a response in the vocal muscle after 4 to 6.6 ms (SD 0.7; mean 5 ms; Fig 3). Magnetic stimulation in the neck produced a MAP that was not statistically different from that obtained electrically (Fig 4). Otherwise, we found a small difference in amplitude and integral of the MAPs induced by opposite surfaces of the coil during cisternal and peripheral stimulation (depending on the flux direction). The main difference in amplitude and integral of the MAPs induced by opposite surfaces of the coil was in cortical stimulation, especially stimulation of the contralateral cortex.

The latency was prolonged up to two or three times as compared to the healthy sides in cases of neurapraxia (Fig 5). In cases of degenerative palsies, either a complete interruption or a difference between distal and proximal stimulation of 25 to 30 ms in latency was found. The values for latency, amplitude, response duration, and peak integral were also compared after cortical, cisternal, and peripheral stimulation, and a good correlation was found between the reduced response, the prolonged latency, and splitting of the MAP with the type of lesion. The difference in amplitude of proximal and distal stimulation varied from 2 to 1 in healthy subjects to 10 to 1 in cases of neurapraxia and 30 to 1 in cases of axonotmesis, if stimulation could be performed. During follow-up of neurapraxic lesions, even 3 to 4 months after complete regeneration a prolonged latency was found as compared to the healthy side, as well as diminished potentials or even the impossibility of stimulation at the cisternal portion, correlating with a

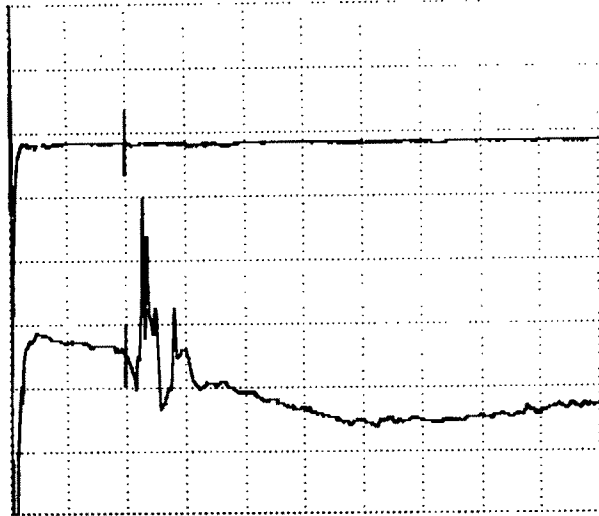


Fig 6. (Case 1) Cisternal magnetic stimulation in central vagus nerve palsy ($500 \mu\text{V}$ per unit; 5 ms per unit).

less excitable or nonexcitable cortical portion.

CASE REPORTS

Case 1. After long-term assisted respiration for polyneuritis, a 46-year-old woman developed recurrent laryngeal nerve palsy on the right side. Electromyography revealed a diminished voluntary activity. Cisternal magnetic stimulation resulted in a prolongation of latency up to 8 ms and a diminished amplitude of MAP (Fig 6). Contralateral cortical stimulation induced a MAP of 26 ms latency. Therefore, a combined central and peripheral vagus nerve lesion was diagnosed.

Case 2. Six weeks after thyroidectomy in a 32-year-old woman, EMG revealed single action potential voluntary activity in a unilateral recurrent nerve palsy. Cisternal magnetic stimulation resulted in a polyphasic MAP after 8 ms latency. A neurapraxic nerve lesion with a good prognosis was diagnosed, and normal function of the vocal cord was regained 4 weeks later.

Case 3. In a 10-day-old infant, inspiratory and expiratory stridor had led to intubation and microlaryngoscopic examination. This revealed a unilateral vocal cord palsy. Cortical magnetic stimulation led to no response. Cisternal and peripheral stimulation induced a MAP after 6.2 and 4 ms, respectively (Fig 7). After reduction of the general anesthesia, some voluntary activity potentials were recorded. Therefore, a premature nuclear area was diagnosed, with an intact peripheral vagus nerve system.

DISCUSSION

The advantages of magnetic stimulation, as compared to well-known electrophysiologic tools such as

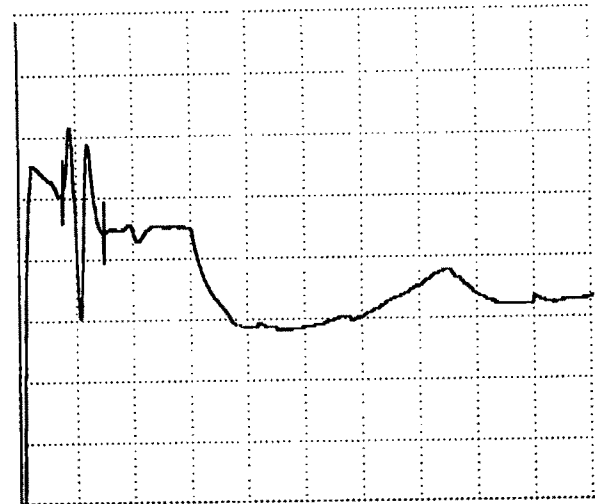


Fig 7. (Case 3) Peripheral magnetic stimulation of vagus nerve with motor action potential in vocal muscle of congenital recurrent nerve palsy ($500 \mu\text{V}$ per unit; 5 ms per unit).

EMG, electrically stimulated NMG, and reflex myography, are based mainly on the possibility of central and intracranial neural stimulation of the lower cranial nerves from cortex to periphery. This allows neurophysiologic investigation also in the early stages of a lower cranial nerve palsy, which up to now has not been possible with the exception of electrically stimulated reflex EMG. Neuromyography with electrical stimuli only shows reliable results at least 6 to 8 days after the onset of a proximal palsy because of a time decay for wallerian degeneration. In contrast, cortical and especially cisternal stimulation of the lower cranial nerves leads to reliable results immediately after the onset of palsy, with the exception of a complete neurapraxic block over a larger distance. The lack of attenuation of an electrical field induced by pulsed magnetic fields results in painless stimulation,¹⁰ which allows stimulation of deep-seated intracranial structures that were not accessible in the awake unanesthetized patient up to the present.

On the other hand, magnetic stimulation is not only feasible in the awake patient, but also in the unconscious or anesthetized patient, and hence is suitable for noncooperative patients and children. Because contact is not required, skin preparation is unnecessary. In addition, intracranial and extracranial neural systems are accessible with the same magnetic stimulation technique and a variety of coil geometries only.¹¹

A present disadvantage of magnetic stimulation is that the site of stimulation of the lower cranial nerves is not readily defined, but as magnetic stimulus increases, there is less dependence on the exact electrode position relative to underlying neural structures. Magnetic stimulation of these lower cranial

nerves with a combination of transoral bipolar hooked wire EMG of the nerve target muscles appears to be a promising technique with minimal discomfort to the patient, and the intracranial segment now appears to be directly accessible to stimulation.

Magnetic stimulation should not be used in patients with epilepsy or after cranial surgery with magnetic material remaining (ie, clips), but it shows no apparent problems or dangers with other subjects.^{7,8}

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DOES INTERVENTION IMPROVE THE NATURAL COURSE OF GLOMUS TUMORS?

A SERIES OF 108 PATIENTS SEEN IN A 32-YEAR PERIOD

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To acquire more insight into the results of treatment versus the "natural" course of glomus tumors, we studied the clinical data of 108 patients, in 58 of whom the disease was hereditary. During a period of 32 years (1956 to 1988), 175 tumors were diagnosed: 52 glomus jugulotympanic tumors, 32 vagal body tumors, and 91 carotid body tumors. The results of radical surgical treatment were disappointing for tumors located at the skull base, ie, nonradical in 59% ($n = 23$) of the cases, but very good for the carotid body tumors, for which 96% ($n = 68$) radical excision was achieved. Moreover, surgery at the level of the skull base dramatically increased morbidity, since it frequently induced cranial nerve palsy. During the follow-up period (maximal observation time 32 years, mean 13.5 years) none of the patients died of residual or recurrent tumor or developed distant metastases, irrespective of the mode and outcome of treatment. When these results are combined with the results of pedigree analysis, a realistic approximation of the "natural" course of the disease for both hereditary and nonfamilial tumors can be made. The results raise the question of whether this natural behavior is really improved by intervention. We conclude that removal of carotid body tumors and solitary vagal body tumors should be considered in order to prevent future morbidity. However, for skull base and bilateral glomus tumors a more conservative monitored "wait and see" policy can be sensible and should be considered in any proposal for treatment of head and neck paragangliomas. When there is serious progression of cranial nerve palsy or when intracranial growth becomes life-threatening, surgical intervention cannot be avoided. The main goal of glomus tumor treatment should be to reduce morbidity rather than trying to increase survival rates.

KEY WORDS — chemodectoma, glomus tumor, hereditary disorders, natural course of disease, paraganglioma.

INTRODUCTION

In the middle of the 18th century Haller was the first to describe the carotid body situated at the medial wall of the common carotid artery at its bifurcation. In 1941, Guild¹ reported "a hitherto unrecognized structure, the glomus jugularis in man," located in the adventitia of the jugular bulb. Rosenwasser² recognized the relationship between an unusual vascular tumor of the middle ear and the normally occurring glomus jugulare body.

One of the main characteristics of glomus tumors (synonyms are nonchromaffin paragangliomas and chemodectomas) is the presence of clusters of tumor cells (*Zellballen*) interspersed among an extensive capillary network. This *Zellballen* system is demonstrated best by silver impregnation of the reticulum fibers.³

As Bartels⁴ mentioned as early as 1949, glomus tumors can also occur as an autosomal dominant hereditary disease. Pedigree analysis showed that tumor expression was restricted to inheritance via the paternal line. This finding is inconsistent with the autosomal dominant transmission assumed before,

but it can be explained in terms of genomic imprinting, ie, the maternally derived gene is inactivated during female oogenesis and can only be reactivated during spermatogenesis. This new genetic theory has considerable implications for genetic counseling in hereditary glomus tumors.⁵ Further genetic studies are currently being performed to localize and identify the predisposing gene defect. Multicentricity, whether unilateral or bilateral, is an important feature of hereditary glomus tumors. It occurs in at least 30% of cases.

The most clinically relevant glomus tumors in the head and neck are the carotid body tumor (CBT), the glomus tympanicum tumor (GTT), the glomus jugulare tumor (the last two are often grouped together as the glomus jugulotympanicum tumor [GJTT]), and the vagal body tumor (VBT).

These benign tumors grow extremely slowly and are associated with a generally low mortality rate, but they can enlarge relentlessly to encompass the adjacent neurovascular structures and even extend intracranially. When surgery is performed on such a large tumor there is an increased risk of neurovascular

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TABLE 1. DISTRIBUTION OF TUMORS BY SIZE CLASS AND LOCALIZATION

Size Class	n	%	GJTT	VBT	CBT
Small	49	40	12	3	34
Intermediate	45	36	6	9	30
Large	30	24	20	2	8
All sizes	124	100	38 (31%)	14 (11%)	72 (58%)

GJTT — glomus jugulotympanicum tumor, VBT — vagal body tumor, CBT — carotid body tumor.

complications as well as of incomplete tumor resection. Almost 75 years ago this risk was already recognized by Balfour and Wildner (as found in Nora et al⁶) when they wrote, "A cure without permanent disability is rare." At that time the complications of surgical treatment were worse than the natural course of the disease itself.

Especially for lesions at the base of the skull, tumor resection frequently leads to considerable and permanent cranial nerve palsy. It is even more difficult to decide whether and when to perform such extensive tumor resection when dealing with bilateral tumors. Therefore, we felt the need to compare the natural course of disease with the outcome of different treatment modalities and studied a series of 108 patients with a total of 175 glomus tumors located in the head and neck region treated in our hospital during the last 32 years.

MATERIALS AND METHODS

PATIENTS

During the past 32 years (1956 to 1988) the diagnosis of glomus tumor was made in 108 patients seen in the Departments of Otolaryngology and Vascular Surgery of the Leiden University Hospital. In 75% of the cases the diagnosis was confirmed histologically. The clinical data in this retrospective study were retrieved from the status reports, which in most cases supplied information on the following items: family history of glomus tumor, age at first diagnosis, presenting signs and symptoms, duration of symptoms, catecholamine secretion, tumor size and localization, multicentricity, mode of treatment, radicalness of surgery, morbidity, and follow-up data. A questionnaire was sent to all 108 patients or relatives (in case of death) requesting additional data on the medical and family histories. Only 3 patients could not be traced or were not informative otherwise. Patients whose response was positive or equivocal with regard to hereditary disease were visited at home to obtain more information about family members who might have had a glomus tumor. In this way 15 families with hereditary glomus tumors were retrieved. Sometimes a family conference or photograph of an ancestor helped to complete the pedigree. The results of this study on the hereditary aspects

have been published elsewhere.⁵ Functioning glomus tumors or extra-adrenal paragangliomas were detected both clinically and on the basis of elevated urinary catecholamine levels. Recently, our group established scintigraphy with labeled metaiodobenzylguanidine as a valuable diagnostic technique for vasoactive paragangliomas.⁷ It is now routinely used in preoperative analysis. Since many patients in our study had multicentric glomus tumors, we prefer to report the follow-up data for individual tumors rather than for patients.

TUMORS

Localization, Size, and Histology. The 108 patients accounted for 52 GJTTs, 32 VBTs, and 91 CBTs, giving a total of 175 glomus tumors. Tumor size had been recorded for 124 glomus tumors. The size of 38 temporal bone glomus tumors (GJTTs) was estimated according to the following semiquantitative categories defined by Rosenwasser.² Small tumors are those confined to the middle ear space without extension in the hypotympanum. These are usually GJTTs arising from the promontory or floor of the tympanum (n = 12). Tumors of intermediate size are those that have penetrated beyond the middle ear in the direction of the mastoid and with involvement of the hypotympanum. This spread indicates that the process originated in the jugular bulb (n = 6). Finally, large tumors are those that show considerable extension into the base of the skull or intracranially (n = 20).

The volume of the VBTs and CBTs (n = 86) was calculated from the dimensions given in the histopathology reports.⁶ Tumor volumes ranged from 1 to 224 cm³. Since no established or uniform classification was available before the introduction of computed tomography (CT), we arbitrarily subdivided tumor volume into three size classes, each of which covered approximately one third of the size range. Tumors measuring between 1 and 18 cm³ (n = 37) were called small, those between 18 and 60 cm³ intermediate (n = 39), and those of 60 cm³ or more large (n = 10). In Table 1 this subdivision is shown for the three tumor sites studied. As described earlier,⁸ all histologic slides of 132 excised tumors were reviewed in light of the current histologic criteria for glomus tumors.³ No histologic sign of malignancy or clinical evidence of distant metastases was found.

Selection of Time Periods. The results of treatment during the past 10 years were compared with those of two earlier 10-year periods. This method for the assessment of trends with respect to tumor resectability and neurovascular complications of surgical management was also used by Hallett et al.⁹

Period 1 (1956 to 1966; 14 patients, 20 tumors)

TABLE 2. INCIDENCE OF FAMILIAL AND NONFAMILIAL TUMORS

<i>Tumor</i>	<i>No. of Patients</i>	<i>M</i>	<i>F</i>	<i>Multiple Tumors (Patients)</i>	<i>Mean Age at Diagnosis With Range (y)</i>
Familial	58 (53%)	28	30	32 (55%)	36 (16-66)
Nonfamilial	50 (47%)	16	34	11 (22%)	45 (12-84)

For both familial and nonfamilial cases, average duration of symptoms at time of diagnosis was about 3 years.

refers to the early days of microscopic ear surgery, when the otologic surgeons obtained their initial experience with glomus tumor surgery and the vascular surgeon had to perform ligation of the carotid artery in some difficult cases.

In period 2 (1967 to 1977; 44 patients, 59 tumors) size and extension of a skull base tumor often had to be estimated clinically with little help from polytomography or angiography. Frequently, surgical management failed to control the tumor in several areas, including the jugular foramen. Repair or grafting of the extracranial carotid artery was possible.

During the past 10 years (period 3, 1978 to 1988; 50 patients, 96 tumors) CT and magnetic resonance imaging (MRI) techniques became widely available, allowing for new and safer surgical approaches to the skull base. In our hospital systematic scanning in the axial and coronal planes became routine in 1984. Furthermore, better preoperative evaluation of cerebral blood flow was introduced.¹⁰ Improved and less invasive imaging techniques are also used more and more to support the traditionally clinical follow-up.

RECONSTRUCTION OF "NATURAL" COURSE OF DISEASE

One of the purposes of this study was to find the most likely approximation of the "natural" course of disease of head and neck paragangliomas. For this, the history of disease of patients treated and followed up in our hospital ($n = 25$) was not sufficient. Especially informative are those patients who live with such a tumor without seeking medical help. We traced 16 such patients from our previous study on hereditary glomus tumors⁵ and observed that many of them had grown old with the disease without dying of it. Those persons or "patients" ($n = 16$) were not initially submitted to diagnosis, treated, or followed up in our own hospital, and information about them was sometimes gathered from family members. For patients with nonhereditary disease these data could be retrieved from the status report and follow-up. Now the course of disease for both hereditary and nonfamilial tumors could be reconstructed from those 1) who were left untreated, 2) with residual tumor after surgery, 3) who had undergone irradiation, or 4) who had a combination of surgery and irradiation.

RESULTS

EPIDEMIOLOGIC DATA

In Table 2 some epidemiologic data for familial and nonfamilial glomus tumors are summarized. In the nonfamilial group (47% of cases) there was a marked female preponderance (68%), in contrast to the familial group, in which multicentricity (55%) was a distinctive feature. It must be noted that the results of this study were gathered retrospectively and that pedigree analysis has influenced the number of familial cases.

For both groups most glomus tumors were diagnosed in the fourth decade of life. At the time of diagnosis the symptoms had been present for 3 years on the average. Note, however, that in 17% of the patients the symptoms had lasted more than 10 years.

PRESENTING SIGNS AND SYMPTOMS

Patients with a GJTT were mainly suffering from hearing loss (88% of cases) and/or pulsating tinnitus (86%). Less frequently (3%) the initial sign was a brisk bleeding from the external auditory canal. Voice change and a facial nerve palsy were each recorded once as a presenting symptom. The classic otologic finding of a mass behind the tympanic membrane, usually with a positive Brown's pulsation sign, was indeed often recorded (32 patients or 64%). Initial cranial nerve deficit was relatively frequent and included the facial (9 patients or 18%), cochlear (9 or 18%), glossopharyngeal (5 or 10%), vagal (7 or 14%), spinal accessory (2 or 4%), and hypoglossal (4 or 8%) nerves.

Vagal body tumors almost invariably presented as a cervical neck mass (25 patients or 89%), which in 18% of cases extended as a pulsating mass into the oropharynx. Cranial nerve dysfunction was less prominent than in GJTTs. The facial and cochlear nerves were never affected, whereas the glossopharyngeal, vagal, spinal accessory, and hypoglossal nerves were involved in 10%, 17%, 3%, and 4% of patients, respectively.

Similarly, a cervical mass at the level of the carotid bifurcation (97%) was the leading sign at the onset of CBTs. Cranial nerve deficit was restricted to the vagal and hypoglossal nerves, in 11% and 4% of the patients, respectively.

TABLE 3. RESULTS OF SURGICAL TREATMENT IN RELATION TO TUMOR SITE AND TIME PERIOD

Years	No. of Patients	No. of Tumors	Glomus Jugulotympanicum Tumor (n = 52)			Vagal Body Tumor (n = 32)			Carotid Body Tumor (n = 91)		
			Radical Surgery	Non-radical Surgery	No Treatment	Radical Surgery	Non-radical Surgery	No Treatment	Radical Surgery	Non-radical Surgery	No Treatment
1956-1966	14	20	2 (28%)	5 (71%)	2	0	1	0	8 (89%)	1	0
1967-1977	44	59	4 (40%)	6 (60%)	3	4 (50%)	4 (50%)	2	25 (96%)	1	8
1978-1988	50	96	10 (45%)	12 (55%)	8	7 (70%)	3 (30%)	9	35 (97%)	1	9
1956-1988	108	175	16 (41%)	23 (59%)	13	11 (58%)	8 (42%)	11	68 (96%)	3 (4%)	17

Five tumors were either irradiated (one vagal body, two carotid body) or embolized (one vagal body, one carotid body).

Thirty glomus tumors (2 GJTTs, 4 VBTs, and 24 CBTs) were detected at a subclinical stage in a search for multicentric tumors. This discovery occurred mainly in period 3 because of the availability of imaging techniques and our special interest in pedigree analysis.

TREATMENT

In 25% of GJTTs, 34% of VBTs, and 18% of CBTs we refrained from treatment because of the extent of the tumor or the age or condition of the patient. Also, in many cases of bilateral disease no treatment was instigated in order to avoid the risk of bilateral cranial nerve palsy. In recent years, we were more and more inclined to prefer such a conservative approach initially, as demonstrated in Table 3, especially for (bilateral) localizations at the skull base. This Table shows that 75% of GJTTs, 59% of VBTs, and 78% of CBTs were treated surgically. Surgery was radical in 41%, 58%, and 96% of cases, respectively.

Recorded data allowed us to determine the relation between tumor size and the results of surgical excision for 116 tumors. As could be expected, large GJTTs are more prone to nonradical surgery than smaller ones, irrespective of the time period. However, for tumors originating from the neck, tumor localization rather than tumor size was predictive for the outcome of surgery (ie, complete removal), which generally appears to have been better than in GJTTs in all three time periods (Table 4).

One VBT and one CBT were embolized as a sole form of treatment. Only in period 1 was radiotherapy (20 to 45 Gy) a treatment modality, used in four patients (GJTT). Three of them required surgical

intervention for the same lesion within 10 years.

COMPLICATIONS OF SURGERY

Surgical removal of GJTTs (n = 39) increased the prevalence of cranial nerve palsy (7th through 12th cranial nerves) more than twofold. For example, facial nerve palsy increased from 20% to 43%, and the prevalence of deafness increased from 18% to 64%. Similar observations were made for the function of cranial nerves IX through XII.

Ninety percent of VBT excisions resulted in loss of function of the 10th cranial nerve, whereas in CBTs, deficits of the 10th and 12th cranial nerves occurred just four times and once, respectively, in 71 excisions.

The carotid artery was ligated four times (CBT), ie, twice in period 1 and in the other periods one time each. One of these patients suffered from transient hemiplegia. Reconstruction of the internal carotid artery was performed four times after CBT removal.

One fatal case occurred in a patient referred to our hospital in 1976, 1 day after the excision of a CBT elsewhere. Revision surgery did not reveal macroscopic damage to the vessels, but the patient remained hemiplegic and died soon afterward.

FOLLOW-UP

Thirty-three GJTTs were available for an average follow-up period of 13.5 years (range, 1 to 32). Thirteen of these were monitored without treatment, while 20 tumors had previously undergone nonradical surgery and three patients were lost to follow-up. All patients in this group are still alive and without serious complaints. Clinically their disease is not

TABLE 4. RESULTS OF TREATMENT IN RELATION TO TUMOR SIZE AND SITE

Size Class	n	GJTT (n = 36)		VBT (n = 14)		CBT (n = 66)		Total Tumors (n = 116)	
		Radical Surgery	Non-radical Surgery	Radical Surgery	Non-radical Surgery	Radical Surgery	Non-radical Surgery	Radical Surgery	Non-radical Surgery
Small	44	6	5	2	1	29	1	37	7
Intermediate	43	2	3	7	2	28	1	37	6
Large	29	6	14	0	2	6	1	12	17

GJTT — glomus jugulotympanicum tumor, VBT — vagal body tumor, CBT — carotid body tumor.

TABLE 5. RECONSTRUCTION OF "NATURAL" COURSE OF DISEASE OF 50 HEREDITARY GLOMUS TUMORS FOUND IN 41 PATIENTS IN RELATION TO TUMOR SITE

Glomus Tumor Type	No. Tumors	No Treatment (17 Pts; AO = 38 y)		Nonradical Surgery (12 Pts; AO = 31 y)		Irradiation (7 Pts; AO = 37 y)		Combination (5 Pts; AO = 35 y)		Overall ADD (y) (41 Pts; AO = 35 y)
		ADD (y)	No. Tumors	ADD (y)	No. Tumors	ADD (y)	No. Tumors	ADD (y)	No. Tumors	
GJTT	21	31	4	17	9	14	4	23	4	20
VBT	9	7	7	16	1	23	1			10
CBT	20	18	14	40	2	25	3	20	1	21
Duration of disease	50	17	25	21	12	19	8	22	5	19

Average age at onset of disease for all treatment modalities was 35 years.

GJTT — glomus jugulotympanicum tumor, VBT — vagal body tumor, CBT — carotid body tumor, AO — average age at onset, ADD — average duration of disease.

progressive, with the exception of one case. This patient had to undergo further surgery within 5 years after incomplete surgical removal. The usual rather indolent clinical course can be illustrated by four cases in which radical cavities show relatively unchanged residual and recurrent glomus tumor tissue 30 years after incomplete removal of the GJTT via a mastoidectomy approach. Unfortunately, follow-up imaging with CT for confirmation of the patient's clinical status was not performed routinely until 1984.

Similar observations can be made on the 20 VBTs, which had a mean follow-up of 7.3 years. Virtually no long-term follow-up data were available for solitary CBTs because of the usually radical excision. Consequently, the untreated CBTs mentioned in Table 3 are mainly accompanied by another paraganglioma at another location. With the help of our medical registry we obtained additional information about patients who had radical surgery in the past and were discharged from further follow-up. From those previously treated for a CBT (n = 68), 8 "patients" had died of unrelated causes, with an average time of 17 years after their initial diagnosis and operation. For those with a GJTT (n = 16), 3 "patients" had died, with an average time of 6 years after surgery for

unrelated causes.

RECONSTRUCTION OF "NATURAL" COURSE OF DISEASE

Especially for hereditary disease, a remarkable observation on the reconstructed course of disease could be made. Including the "patients" (n = 16) from the pedigrees, we collected a group of 50 tumors (41 patients), which we subdivided into four groups: 1) those left untreated; and those treated with 2) nonradical surgery, 3) irradiation, or 4) both surgery and irradiation. The average duration of disease was about 19 years irrespective of tumor site, as is illustrated by Table 5. Also for this group (ie, affected family members or "patients"), a marked increase in cranial nerve palsy was most clearly observed in patients who underwent surgery. For example, in 4 of 9 patients with GJTts the operation induced an increased deficit of the 7th, 8th, and 10th cranial nerves, and 3 of them also revealed new deficits of the 9th, 11th, and 12th cranial nerves. Three patients showed no adverse effects of surgery, and in the other 2 no reliable information was available.

As demonstrated by Table 6, similar observations were made for nonfamilial tumors, for which the average course of disease was about 13 years.

TABLE 6. RECONSTRUCTION OF "NATURAL" COURSE OF DISEASE OF 35 NONHEREDITARY GLOMUS TUMORS FOUND IN 31 PATIENTS IN RELATION TO TUMOR SITE

Glomus Tumor Type	No. Tumors	No Treatment (9 Pts; AO = 52 y)		Nonradical Surgery (20 Pts; AO = 43 y)		Combination (2 Pts; AO = 44 y)		Overall ADD (y) (31 Pts; AO = 46 y)
		ADD (y)	No. Tumors	ADD (y)	No. Tumors	ADD (y)	No. Tumors	
GJTT	22	7	7	16	14	16	1	13
VBT	9	2	2	13	6	25	1	12
CBT	4	9	2	19	2			14
Duration of disease	35	6	11	15	22	21	2	13

Average age at onset of disease for all treatment modalities was 46 years.

GJTT — glomus jugulotympanicum tumor, VBT — vagal body tumor, CBT — carotid body tumor, AO — average age at onset, ADD — average duration of disease.

In our study we included 12 patients with familial and 4 patients with nonfamilial glomus tumors who had an age at onset of disease of under 30 years (average follow-up, 17 and 19 years, respectively). With the exception of 1 patient who died of disease, we did not observe any significant difference in the course of disease between these patients and the ones with a later age at onset.

DISCUSSION

The current study is comparable to the five largest studies in the literature with regard to the number of cases reported (range, 74 to 231) and the duration of follow-up (range, 1 to 27 years).^{9,11-14} Also, the number and nature of signs and symptoms are consistent with these earlier reports. The mean age at onset of disease was 33 years for the familial group and 44 years for the nonfamilial group; these means are in accordance with the literature.^{5,15} It seems likely that familial cases are diagnosed earlier, as the family is aware of the possibility of the disease.

However, the observed incidence of familial glomus tumors (50%) is much higher than in most other series,¹⁵⁻¹⁷ where it is about 10%. Partly this may be attributed to the relatively close-knit communities in which families tend to dwell in the region near our institution. Probably it is also due to our screening procedure, which focused on the familial aspects of glomus tumors. We demonstrated that genomic imprinting may account for the finding that inheritance is almost exclusively via the paternal line.⁵

Familial occurrence of glomus tumors is often accompanied by multicentricity.^{15,16} Our zeal to detect additional tumors will have contributed to an unusually high percentage (55%) of multicentric tumors.

The possibility that the multicentric occurrence of glomus tumors should be explained as metastatic disease has been invalidated by the results of our recent DNA ploidy study.⁸ With flow cytometry we could not find any arguments for a common cellular origin of different tumor sites in patients with multifocal, hereditary disease.

The biologic behavior of this tumor is highly intriguing. Although roughly 40% of the cases show frank DNA aneuploidy, this finding is not associated with the development of either metastatic disease or an aggressive growth pattern.⁸ Thus, the question remains as to which factors prevent these tumors from progressing to overt malignancy. As a matter of fact, the incidence of malignancy in glomus tumors as indicated by lymphogenic and hematogenic metastases is probably not greater than 10%.³ These tumors may

penetrate into nerves and bone tissue, but local infiltration is not correlated with the occurrence of distant metastases.¹⁸ We observed just one malignant laryngeal paraganglioma, which caused massive metastatic disease 2.5 years after the initial diagnosis.¹⁹

In the present series, angiography was used in almost all patients as the main diagnostic technique since 1962. It was accompanied by CT scanning for lesions at the skull base since 1977. From 1984 we scanned more and more routinely in two perpendicular planes. In 1987 we implemented MRI, because it provides superb soft tissue contrast if gadolinium-diethylenetriamine pentaacetic acid enhancement is used and offers the possibility of scanning in the sagittal plane. It is particularly useful for the assessment of the intracranial extent of the tumor.²⁰ We are currently using it as a noninvasive screening technique in a study on familial glomus tumors.

In the past surgeons often had to remove GJTTs piece by piece, inducing tremendous bleeding and damage to adjacent neurovascular structures.²¹ Complete surgical removal of GJTTs was usually extremely difficult because of their location in the petrous bone and the impossibility of knowing the true extent of the lesion in advance. Therefore, these neoplasms were known for their high recurrence rate. We share the opinion of Glasscock et al²² that the early literature must be regarded with a certain amount of skepticism.

The development of the infratemporal fossa approach by Fisch²³ greatly improved the completeness of GJTT resection at the skull base. Techniques for safe resection of CBTs are based on excision in the adventitial plane, from which the blood supply of the tumor is derived.²⁴

In 1969 McCabe²⁵ advocated the notion that the size and extent of the tumor is decisive for the selection of the most appropriate form of therapy. Unfortunately, this information could not be obtained before the introduction of CT scanning in 1977. Since many surgical classifications for GJTTs are based on CT scanning data,^{12,13} it is not possible to apply any of these classifications in the current review over the past 32 years.

Our surgical results for GJTTs (59% nonradical) are comparable with those in the literature,^{2,14,17,26} with the exception of a few series^{12,13,22} that claim better results. Our preliminary results with the infratemporal fossa approach (seven tumors) were more favorable, but conclusions with regard to surgical morbidity are not yet permitted. It is conceivable that even large GJTTs with involvement of the internal carotid artery at the skull base can be resected

completely with this technique.¹⁰

With 96% radical excision of CBTs, our results were comparable to those reported by other authors,^{6,9} as were the numbers of vascular and neurologic postoperative complications of CBT and VBT excision. The position of irradiation in the management of glomus tumors is still heavily debated.²⁷ Several authors have claimed a high efficacy of radiotherapy in the control of these slow-growing tumors.²⁸⁻³⁰ Others use it in elderly patients or in individuals in poor health to slow down local tumor growth. The response of these vascular tumors to irradiation is limited to microvascular damage, leading to sclerosis and fibrosis, since a direct cell-killing effect cannot be demonstrated.²⁸ The histopathologic study done by Hawthorne et al³¹ showed that tumor behavior after irradiation is unpredictable. They investigated 18 tumors requiring surgery after irradiation and detected vital tumor tissue without signs of necrosis in 12. This observation clearly supports the vast experience of Rosenwasser²: "The longer an irradiated patient is followed clinically, the more likely the recurrence."

The relatively large number of tumors in our series that had not been treated is explained by the high number of bilateral tumors in our series. This high number is due to the high percentage (50%) of familial glomus tumors, which are often multicentric (see Introduction). In order to avoid bilateral cranial nerve palsy, we decided to operate on the second side only if the first resection had not caused essential cranial nerve palsy. When we refrained from surgery in recent years, we relied on a "wait and see" policy under the control of CT and MRI in preference to irradiation, for the reasons mentioned below.

In this retrospective semiquantitative study covering many years we made a comparison between the results of the different therapeutic modalities and the usually indolent natural course of the disease, rather

than comparing the follow-up of radically and nonradically treated patients. From Tables 5 and 6, it follows that survival cannot be improved by any treatment, since the vast majority of patients with hereditary and nonhereditary disease have a close to normal life expectancy. The surgically treated group showed the most complications. Although it may not be concluded from these data that treatment increased morbidity, one may ask whether the patients did benefit from (nonradical) surgery or other treatment. In view of this, results reported in the literature for treatment and follow-up of glomus tumors (both of surgery and irradiation) may well have been influenced by the course of the disease. Certainly, in our series there are exceptions, too, in which tumor progression is far more rapid. This makes the decision to refrain from intervention even more difficult, especially in young people. However, from our material it cannot be concluded that patients with an early onset of disease do have a more severe outcome. Unfortunately, at present we have no tumor-biologic marker at our disposal that can predict the growth pattern.

CONCLUSION

In general, our series demonstrates that surgical removal of CBTs and solitary VBTs is quite possible without major complications. Usually it prevents future morbidity, since the resection is almost always radical. On the other hand, we feel that for GJTTs a monitored "wait and see" policy can be sensible and is justified by the morbidity frequently induced by surgery and the observation that survival is not improved by any treatment. Once a skull base tumor is causing progressively invalidating cranial nerve palsy or it becomes life-threatening because of intracranial extension, surgical intervention should be undertaken. At this point both the surgeon and the patient will be convinced that this decision and its consequences are inevitable. With bilateral tumors we propose a similar strategy.

ACKNOWLEDGMENT — We thank J. Hermans for his support in data analysis.

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THIRD INTERNATIONAL CONFERENCE ON PEDIATRIC OTORHINOLARYNGOLOGY

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OFF-VERTICAL AXIS ROTATION: A TEST OF THE OTOLITH-OCULAR REFLEX

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The vestibulo-ocular reflex was studied via off-vertical axis rotation (OVAR) in the dark. The axis of the turntable could be tilted from vertical by up to 30°. Eye movements were measured with electro-oculography. Results from healthy asymptomatic subjects indicated that 1) a reliable otolith-induced response could be obtained during constant velocity OVAR using a velocity of 60°/s with a tilt of 30°; 2) constant velocity OVAR rotation was nausea-producing and, especially if subjects were rotated in the dark about an earth-vertical axis prior to being tilted, disorienting; and 3) sinusoidal OVAR produced minimal nausea; the eye movement response appeared to be the result of a combination of semicircular canal and otolith components. We conclude that OVAR has the potential of becoming a useful method for clinically assessing both the otolith-ocular reflex and semicircular canal-otolith interaction.

KEY WORDS — otolith organs, rotational testing, vestibulo-ocular reflex.

INTRODUCTION

Peripheral vestibular sensors consist of the otolith organs, which sense linear acceleration, and the semicircular canals, which sense angular acceleration. In order to clinically evaluate the semicircular canals, in particular the horizontal semicircular canals, we stimulate either one horizontal canal (alternate caloric stimulation) or both together (conventional rotational testing), and rely on the vestibulo-ocular reflex to provide a "readout" of vestibular activation using eye movements. It is much more difficult to create a specific test for the otolith organs. The human otolith-ocular reflex has been studied by using earth-vertical axis rotation with the head eccentric from the axis of rotation,^{1,2} counterrotation in a centrifuge,³ linear acceleration on a sled or parallel swing,^{4,5} and off-vertical axis rotation (OVAR).⁶⁻⁹ Although these various methods of stimulating the otolith-ocular reflex have been used in research laboratories and in aerospace medicine, at present there are no established methods for assessing the otolith-ocular reflex suitable for a clinical laboratory environment.

Off-vertical axis rotation entails whole body rotation about an axis that is inclined with respect to gravitational vertical. Typically, subjects are oriented such that their rostral-caudal body axis is aligned with the axis of rotation to produce yaw rotation as in conventional earth-vertical axis rotational testing.⁶⁻⁹ We chose to investigate OVAR, employing tilt angles of up to 30°, because it appeared to have several advantages as an otolith-ocular reflex test suitable for

the clinical vestibular laboratory: 1) the stimulus can be delivered in a reliable, repeatable fashion to a large variety of patients, 2) it can be delivered by a conventional earth-vertical axis rotation chair with minor modifications, 3) this test can be combined with visual inputs to evaluate visual-vestibular interactions, and 4) it can be used to stimulate the otolith organs alone (using constant velocity rotation) or in combination with the semicircular canals (using nonconstant velocity rotations, eg, sinusoids).

Previous studies of OVAR have suggested that this method of stimulating the otolith-ocular reflex could form the basis of a clinically useful tool.^{10,11} However, nausea during testing, the small magnitude of the eye movement response, and high response variability may reduce the clinical utility of OVAR. The goal of this study was to address these limitations as part of an ongoing effort to develop a protocol suitable for evaluating the clinical usefulness of OVAR. We investigated three issues: 1) the influence of angle of tilt and rate of rotation during constant velocity OVAR on eye movement response and nausea, 2) the effect of starting the OVAR stimulus with the axis tilted versus tilting the axis during rotation, and 3) the effects of sinusoidal versus constant velocity rotation about an off-vertical axis.

METHODS

Twenty-one subjects (13 men and 8 women, 19 to 69 years of age) participated in this study. All of the subjects participated on a voluntary basis after testing

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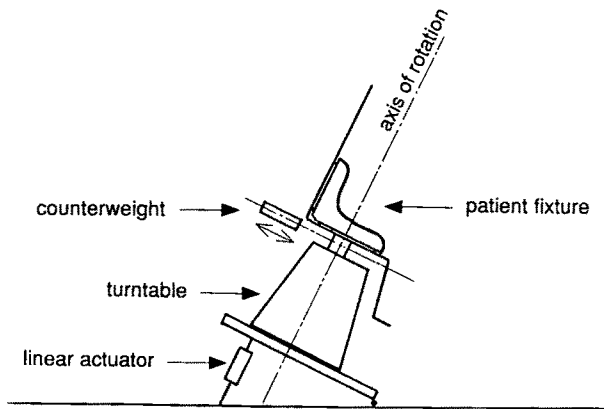


Fig 1. Diagram of off-vertical axis rotational chair. Linear actuator allows tilt of up to 30°. Counterweight is used to minimize fluctuations in torque required to provide constant angular velocity.

was fully explained to them by a qualified research assistant, and they signed an informed consent form approved by the Institutional Review Board of the Eye and Ear Institute of Pittsburgh. Before undergoing OVAR testing, each subject underwent the battery of tests described below. Exclusionary criteria consisted of eye movement or postural responses outside of normal limits for our laboratory on the following tests:

1. An ocular motor screening battery that consisted of a search for nystagmus both with and without fixation and with horizontal and vertical gaze deviation, and an assessment of saccades, pursuit, and optokinetic nystagmus.
2. A search for static positional nystagmus in the supine, head right, head left, right lateral, and left lateral positions with eyes open in the dark.
3. Responses to alternate binaural bithermal caloric irrigation using a closed-loop irrigator (Grams Medical Products, Costa Mesa, Calif) with water at 27°C and 44°C. Normal limits for our laboratory are a reduced vestibular response of 25% and a directional preponderance of 30%.
4. Dynamic posturography using Equitest (Neurocom International, Clackamas, Ore).

Additional baseline testing of each subject included earth-vertical axis rotation with sinusoids and trapezoids. Earth-vertical axis sinusoids were performed at 0.02, 0.05, 0.1, and 0.5 Hz at 50°/s peak velocity. Earth-vertical axis trapezoids were performed at 60°/s both clockwise and counterclockwise, both with and without postrotatory head tilt. Typically, the screening and baseline studies required two separate visits and were performed prior to OVAR testing, which required a third test session.

The OVAR testing was performed with a device

designed and built at the Eye and Ear Institute of Pittsburgh. The OVAR device (Fig 1) consists of a rotation chair affixed to an 80 foot-pound turntable attached to a tilt stand. Rotation rate was driven by a PDP 11/73 digital computer (Digital Equipment Corp), while angle of tilt was controlled manually by using a hydraulically powered linear actuator. The rate of tilt was 1.5°/s for all protocols, with the total tilt 30° or less. Affixed to the rotation chair was a head restraint device that ensured minimal relative motion between the head and the rotation chair. Eye movements in the dark were measured by using DC-coupled electro-oculography and an optically isolated preamplifier (Templin Engineering); eye movements were recorded on a chart recorder and sampled by the 11/73 computer at 100 Hz. The electro-oculography signal was calibrated by asking each subject to gaze at targets placed 10° to the left and right of center.

The OVAR stimulation was produced by tilt following rotation (R,T) or rotation following tilt (T,R); T,R trials used either a constant or a sinusoidal rotational velocity. These OVAR protocols are depicted in Fig 2. Figure 2A,C illustrates the T,R paradigm in which the subject is first tilted into the nose-up position with the chair locked rotationally and subsequently rotated at a constant velocity (Fig 2A) or sinusoidally (Fig 2C). For T,R constant velocity trials, rotation was continued for approximately 90 seconds, thereby allowing the initial exponential decay of slow-component velocity (SCV) to abate and the modulation and bias components to be assessed. For sinusoidal rotations, testing was performed at 0.02, 0.05, 0.1, and 0.5 Hz at 50°/s peak velocity. At least three complete cycles of stimulation were delivered at each frequency. Figure 2B illustrates the R,T paradigm in which subjects are rotated at a constant velocity about an earth-vertical axis for approximately 90 seconds to allow the semicircular canal response to decay. Then, subjects are tilted to a predetermined tilt angle. Subjects were not told exactly when they would be tilted; they were, however, questioned repeatedly regarding their feelings of discomfort during testing.

After each OVAR trial, a motion sickness score was assigned. We used the scoring system shown in Table 1, which was adapted from the motion sickness assessment scheme developed by the Massachusetts Institute of Technology Man-Vehicle Laboratory (C. Oman, personal communication, 1989).

The eye movement response to OVAR was analyzed by first passing the eye position data through a nystagmus algorithm that identified the quick components of the nystagmus, interpolated across the quick-component epochs, and then numerically dif-

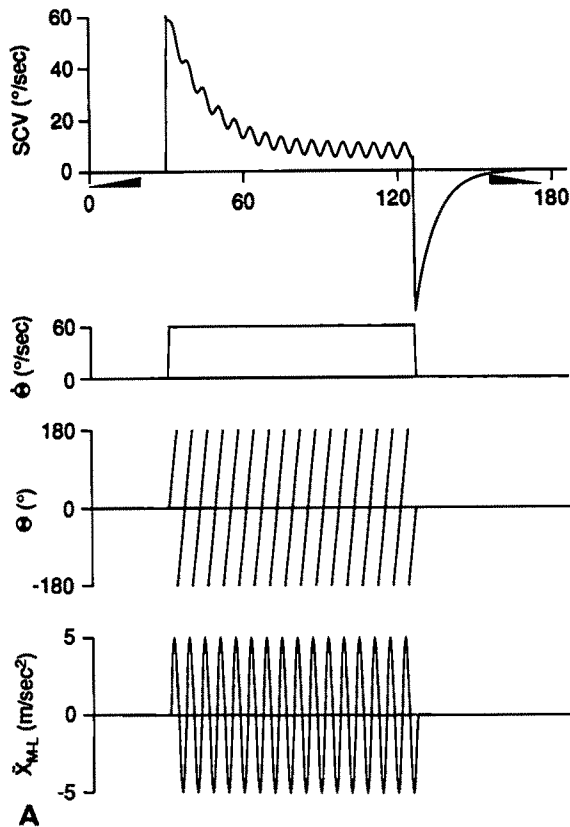
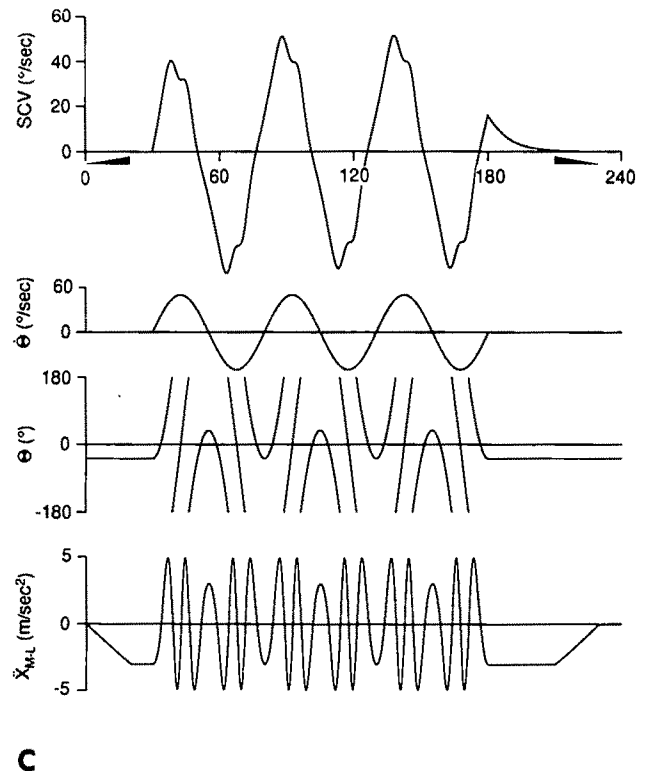
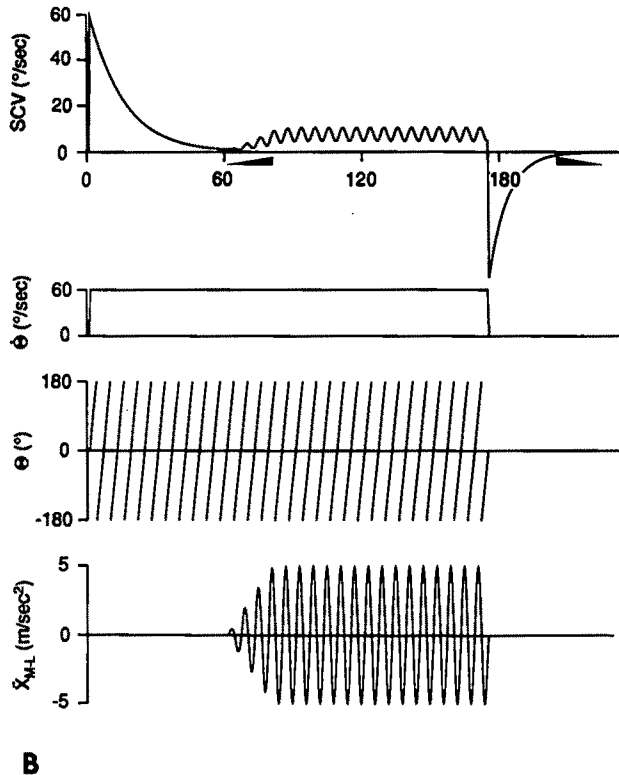


Fig 2. Diagrammatic representations of off-vertical axis rotation stimuli and slow-component eye velocity (SCV) responses. Top trace in each panel shows SCV versus time. Second trace shows rotational chair velocity (Θ). Third trace shows angular position of subject with 0° indicating nose-up and plus (+) and minus ($-$) 90° indicating right ear down and left ear down, respectively. Bottom trace indicates effective linear acceleration along subject's mediolateral axis (presumed otolith stimulus). Shaded wedges underneath SCV traces indicate time course of tilt up and tilt down. A) Constant velocity paradigm in which axis of rotation is tilted so that subject reaches nose-up position prior to onset of rotation. Note that eye movement response consists of initial rapid increase in eye velocity followed by exponential decay to nonzero bias with superimposed periodic modulation. B) Paradigm in which subject is rotated about earth-vertical axis at constant velocity for approximately 90 seconds prior to onset of tilt. Once subject has been tilted, bias and modulation components develop. C) Sinusoidal paradigm in which axis of rotation is tilted prior to onset of sinusoidal rotation. Rotational position of subject is designed to be symmetric about nose-up position. Note that SCV consists of periodic waveform at frequency of rotation with additional higher-frequency components due to complex otolith stimulus.



ferentiated the cumulative slow-component eye position to estimate SCV. The SCV data were then averaged within 100-millisecond bins (10 points).

Constant velocity OVAR induces a continuous

nystagmus whose SCV contains a nonzero baseline, the bias component, and a periodic fluctuation at the frequency of rotation, the modulation component.⁸ For the constant velocity T,R trials, we estimated the

TABLE 1. MOTION SICKNESS POINT SYSTEM FOR USE WITH OFF-VERTICAL AXIS ROTATION

		Mild	Moderate	Severe
Minor symptoms				
Epigastric awareness	1			
Dizziness	1			
Flushing or red face	1			
Headache	1			
Graded symptoms				
Nausea		2	4	8
Salivation		2	4	8
Sweating		2	4	8
Pallor		2	4	8
Retching or vomiting	16			

size of the bias and modulation components by fitting the following equation through the data using a nonlinear iterative least squares regression algorithm¹²:

$$(1) \text{scv}(t) = \text{amp} \times \exp(t/\tau) + \text{bias} + \text{modamp} \times \sin(2\pi/T + \phi)$$

where amp and τ are the amplitude and time constant of the initial exponential decay of the SCV, bias is the magnitude of the bias component, modamp and ϕ are the magnitude and phase of the modulation component, and T is the period of rotation. The initial conditions for the iterative algorithm for amp, τ , and bias were obtained by least squares fitting an expo-

ponential plus offset through the first 20 seconds of data; the initial conditions for modamp and ϕ were obtained by fitting a sinusoid plus offset through the last 30 seconds of data.

To refine the fit, the standard deviation of the residual (ie, the difference between the data and the fit) was computed. Each data point was then compared with the fit plus and minus three times the standard deviation of the residual to identify wild points. These wild points were typically related to quick components that were not removed by the nystagmus algorithm described above. All wild points were removed from further data processing, and the fit was recomputed by using the current fit parameters as initial conditions. This wild point editing procedure was performed iteratively until no additional wild points were identified.

For the R,T trials, we assumed that the SCV was, after a short time, composed of only bias and modulation components. We fit, using least squares, the following equation through the final 30 seconds of data:

$$(2) \text{scv}(t) = \text{bias} + \text{modamp} \times \sin(2\pi/T + \phi)$$

where bias, modamp, ϕ , and T are as above in equation 1. The wild point editing procedure described above was again used iteratively.

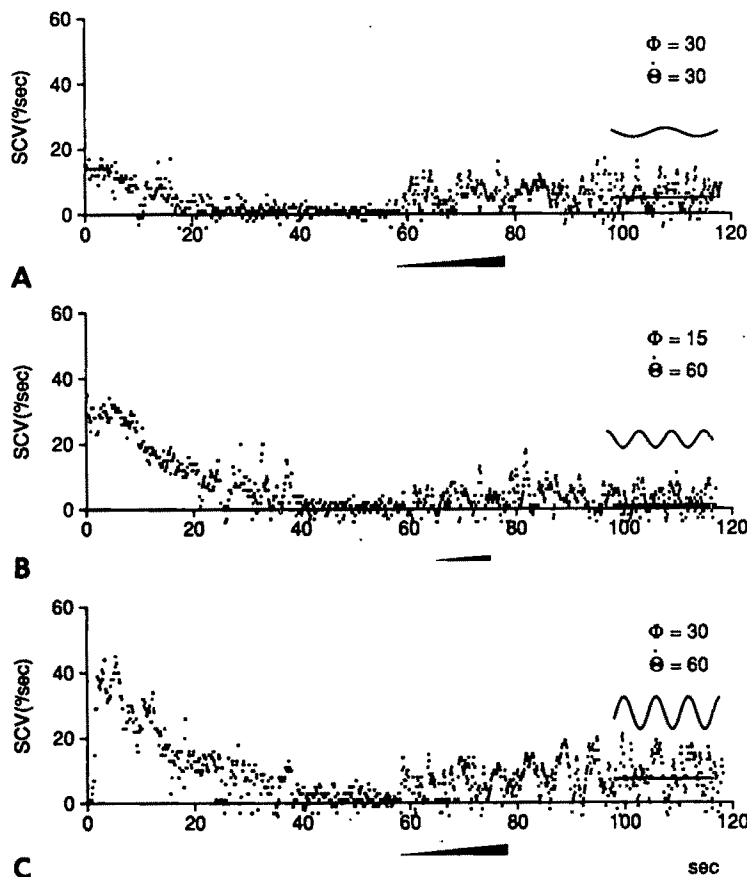


Fig 3. Representative slow-component eye velocity (SCV) response to constant velocity off-vertical axis rotation of three stimulus strengths using paradigm in which rotation precedes tilt. All data were obtained from same subject. For illustrative purposes, SCV data were smoothed by using three-point median filter.¹⁴ Estimated bias component is indicated by horizontal line drawn through last 20 seconds of data; sinusoid above data represents estimated modulation. A) Tilt of 30°, velocity of 30°/s. B) Tilt of 15°, velocity of 60°/s. C) Tilt of 30°, velocity of 60°/s.

TABLE 2. EFFECT OF STIMULUS MAGNITUDE ON OTOLITH-OCULAR RESPONSES TO CONSTANT VELOCITY OFF-VERTICAL AXIS ROTATION

	Modulation Component (°/s)		Bias Component (°/s)	
	At 30°/s Rotation	At 60°/s Rotation	At 30°/s Rotation	At 60°/s Rotation
15° Tilt	—	1.7 ± 0.4 (N = 5)	—	1.1 ± 0.7 (N = 5)
30° Tilt	1.2 ± 0.1 (N = 3)	5.8 ± 2.4 (N = 16)	1.9 ± 0.3 (N = 3)	4.3 ± 2.8 (N = 16)

Data represent mean ± SD.

As Figure 2C illustrates, the tilt-induced linear acceleration produced by sinusoidal OVAR has a complex time course; the expected SCV will contain a (semicircular canal) sinusoidal component at the rotation frequency plus higher-frequency (otolith) linear acceleration components. For the purpose of this initial study, we chose to investigate what effect the addition of an otolith stimulus has on the angular semicircular canal response; we did not try to analyze the otolith component directly. Accordingly, we fit the response, using least squares, with a sinusoid at the stimulus frequency and obtained estimates of sinusoidal amplitude and phase for each stimulus cycle using

$$(3) \quad \text{scv}(t) = A \sin(2\pi f t + \phi)$$

where A is the amplitude of the sinusoid, ϕ is the phase, and f is the frequency of the sinusoidal rotational stimulus velocity. The wild point editing procedure described above was again used iteratively. Both A and ϕ were averaged across as many cycles of data as were available, typically two cycles for 0.02 Hz and four cycles for 0.05 Hz. Gain and phase were

computed with respect to stimulus velocity. The higher-frequency components, presumably otolith-induced, that were observed in the eye velocity response to the lowest stimulus frequency were of small magnitude and were ignored for this study.

RESULTS

Three separate studies were undertaken to address the following issues: 1) the sensitivity of the otolith-ocular reflex to various constant velocity OVAR protocol stimulus parameters, 2) the response to R,T as compared to constant velocity T,R OVAR, and 3) the response to sinusoidal as compared to constant velocity OVAR. In preliminary experiments¹³ we tested various combinations of tilt angle (10°, 20°, and 30°) and rotation rate (10°/s, 30°/s, and 60°/s) and found that the lower values of tilt and rotation rate were not effective in producing reliable responses. We then attempted to quantitate the sensitivity of OVAR responses to stimulus intensity by using three R,T paradigms: 1) 30° tilt and 60°/s rotational velocity, 2) 15° tilt and 60°/s rotational velocity, and 3) 30° tilt and 30°/s rotational velocity. Eight subjects were tested, including four men and four women, 24 to 49 years of age. The responses to these three OVAR stimulus paradigms are shown for one subject in Fig 3.¹⁴ Table 2 indicates the magnitude (mean ± 1 SD) for both the modulation and the bias components for the three sets of stimulus parameters. Because not all subjects were able to complete each paradigm in both directions, the number of data points differs for each cell. The N for each cell represents the total number of trials for that stimulus magnitude, including both clockwise and counterclockwise trials. It can be seen

Fig 4. Comparison of slow-component velocity (SCV) responses to constant velocity paradigms using tilt of 30° and rotational velocity of 60°/s. Decaying exponential and sinusoids shown as solid lines represent best fit to initial exponential decay and modulation components, respectively. Data were obtained from two different subjects. Estimated bias component is indicated by horizontal line drawn through last 20 seconds of data. For illustrative purposes, SCV data were smoothed by using three-point median filter.¹⁴ A) Tilt followed by rotation. B) Rotation followed by tilt.

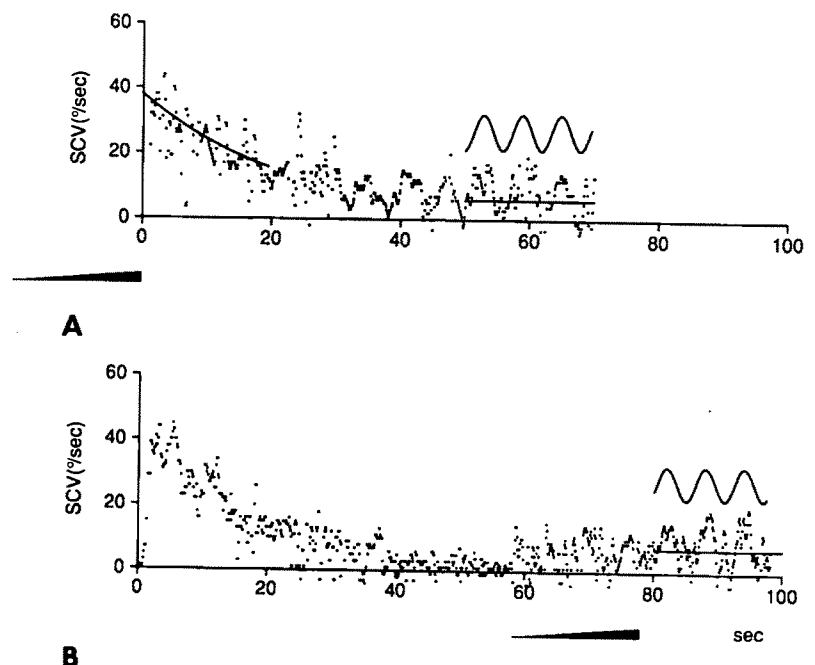


TABLE 3. COMPARISON OF ROTATION AT 60°/s FOLLOWING 30° TILT TO THAT AT 30° TILT FOLLOWING 60°/s ROTATION

	R,T	T,R
Modulation component (°/s)	5.8 ± 2.4 (N = 16)	5.6 ± 3.0 (N = 14)
Bias component (°/s)	4.3 ± 2.8 (N = 16)	5.13 ± 5.0 (N = 14)

Data represent mean ± SD of otolith-ocular response to constant velocity off-vertical axis rotation.
R,T — rotation followed by tilt, T,R — tilt followed by rotation.

that at the highest stimulus magnitude the mean of the response parameters was more than twice that at the lower stimulus magnitudes. Even though response variability was high, with a standard deviation equaling about half of the mean for both the modulation and bias components at 30° tilt, 60°/s rotational velocity, the modulation component for the tilt 30° and velocity 60°/s was statistically different from the modulation component for the other two conditions ($p < .05$; one-way analysis of variance; Tukey multiple post hoc comparisons¹⁵). The differences in bias component magnitudes for the three protocols were not statistically significant ($p > .05$).

As described previously, there are two methods for achieving OVAR: one can tilt the axis first and then begin rotation (the T,R paradigm), or one can tilt the axis of rotation while a subject is rotating (the R,T paradigm). When used with constant velocity rotation, each has theoretic advantages and drawbacks: R,T allows the experimenter to delay the tilt until the semicircular canal response has decayed sufficiently and study the otolith responses directly, while T,R allows one to observe possible otolith-induced modifications of the canal response. In addition, the subjective sensations of the two responses are likely to be different, especially because the R,T paradigm induces "Coriolis forces," which are known to be

nausea-producing.¹⁶

To examine whether the two paradigms produced different objective estimates of otolith function (bias and modulation components) or induced different subjective sensations, we compared the responses of a group of seven subjects (four men and three women, 25 to 69 years of age) to T,R in both clockwise and counterclockwise rotations with the responses of a group of eight subjects (four men and four women, 24 to 49 years of age) to R,T in both directions; this latter group was also used in the previous sensitivity study. We were unable to perform a matched pairs study because of the reluctance of many of the subjects to return for repeated OVAR testing. A velocity of 60°/s and a tilt angle of 30° were used for both protocols. Responses for the two paradigms were of similar magnitude (Fig 4¹⁴), although the variability of the response was less for the R,T studies (Table 3). Unpaired *t* tests indicated no significant effect of R,T versus T,R ($p > .05$). An objective assessment of motion sickness showed no differences between the two paradigms; motion sickness scores during R,T studies exceeded 10 in two of eight subjects, while for constant velocity T,R studies, motion sickness scores exceeded 10 in three of seven subjects. However, because of the unusual perceptions of motion during the R,T paradigm, such as feeling inverted, the R,T paradigm was perceived to be more bothersome than the constant velocity T,R paradigm. For both the R,T and the constant velocity T,R paradigms, subjects noted increased motion-induced discomfort during those trials in which the direction of rotation differed from the direction of the preceding trial.

The third study evaluated the response to the sinusoidal T,R paradigm wherein the rotational velocity followed a sinusoid. Rotations were delivered at 0.02, 0.05, 0.1, and 0.5 Hz with a peak velocity of

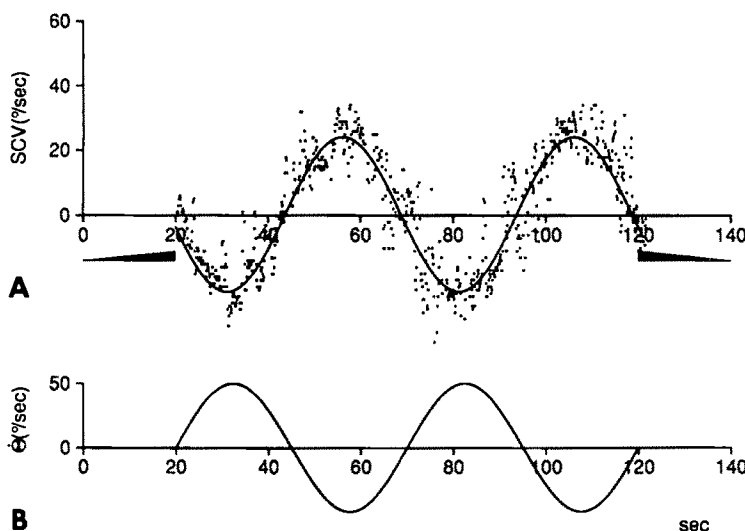


Fig 5. Representative slow-component eye velocity (SCV) response to sinusoidal trial (tilt followed by rotation) using tilt of 30° and rotation at 0.02 Hz, 50°/s peak velocity. Solid line drawn through data represents best fit at frequency of stimulation. For illustrative purposes, SCV data were smoothed by using three-point median filter.¹⁴ A) SCV data. B) Rotational chair velocity ($\dot{\theta}$).

TABLE 4. EYE MOVEMENT RESPONSES TO SINUSOIDAL EARTH-VERTICAL AXIS AND OFF-VERTICAL AXIS ROTATION

	0.02 Hz		0.05 Hz	
	EVAR	OVAR	EVAR	OVAR
Gain	0.41 ± 0.14	0.24 ± 0.10	0.52 ± 0.14	0.31 ± 0.16
Phase	20.3 ± 6.2	25.4 ± 11.2	5.7 ± 2.9	3.3 ± 7.4

N = 7 for all measures. Data represent mean ± SD.
EVAR — earth-vertical axis rotation, OVAR — off-vertical axis rotation.

50°/s. Subjects were placed so that their average position during each stimulus cycle was nose-up. This was accomplished by using a starting position for each rotation that equaled half the rotational position amplitude of the stimulus and by rotating subjects toward the nose-up position at the start of rotation (Fig 2C). For this study we used the same population (N = 7) as that used in the constant velocity T,R study described above. All subjects completed testing: motion sickness scores did not exceed 2. Comments from the test subjects indicated that low-frequency sinusoidal OVAR was more bothersome than high-frequency OVAR; rotation at 0.02 Hz, the lowest test frequency, was the most nausea-producing sinusoidal OVAR stimulus.

Shown in Fig 5¹⁴ is the response at 0.02 Hz for a single subject. Table 4 gives gain and phase values for OVAR and for earth-vertical axis rotation at the two lowest test frequencies. Statistical analysis using paired *t* tests indicated that gain during OVAR was significantly ($p < .05$) less than gain during earth-vertical axis rotation at both frequencies; the difference was highly significant ($p < .01$) at 0.02 Hz.

DISCUSSION

We agree with an earlier statement⁶ that to see reliable bias and modulation OVAR responses in humans, tilts of at least 30° and constant velocities of about 60°/s are needed. Our study extends knowledge regarding the human response to OVAR: 1) tilt following constant velocity rotation (R,T), and constant velocity rotation following tilt (constant velocity T,R) provide quantitatively similar eye movement responses; 2) although both R,T and constant velocity T,R are nausea-producing, R,T may produce unusual and more distressing illusions of motion; and 3) sinusoidal OVAR produces a surprisingly minimal amount of nausea and induces an eye movement response that appears to differ systematically from

sinusoidal earth-vertical axis rotation.

The development of an otolith-ocular reflex test that provides reliable information about the integrity of the otolith organs has obvious clinical value. Many vestibular disorders are of unknown cause; the ability to determine whether or not the otolith organs are involved would add to clinical assessment of both peripheral and central vestibular disorders. Because of its ability to stimulate the otolith organs, OVAR could be used for such a purpose. The results of this study indicate that by appropriate choice of stimulus protocol and stimulus magnitude, measurable otolith-induced eye movement responses can be obtained, and nausea and subject discomfort can be kept at an acceptable level. The results of our limited study would indicate, however, that OVAR response variability is high. This high variability in response parameters was found despite the fact that our subject population could be considered "supernormal" in the sense that strict exclusionary criteria were used to select subjects.

Further research will be aimed at developing stimulus protocols that induce responses with less variability while still being tolerable for the subjects. In this regard, preliminary data from Zimberg et al¹¹ (1991) suggest that R,T protocols of shorter duration are worthy of further study. A natural question that arises when using shorter protocols is the stationarity of the response. Does the initial response have a value different from the steady state value, which could bias the results of shorter protocols? To test this, we reanalyzed our R,T responses, breaking the 60-second epochs into thirds and halves. We found no significant differences among the responses during these various epochs. These findings suggest that shorter exposures to OVAR will yield unbiased estimates of the parameters of the otolith-ocular reflex.

Off-vertical axis rotation is also a potential tool for assessing semicircular canal-otolith interaction. This might be particularly useful in patients with presumed central vestibular disorders, in whom the processing of canal and otolith information may be impaired.

Precisely how OVAR testing might fit into the clinical laboratory assessment of patients with dizziness and balance disorders remains to be determined. Further research, including the testing of both normal subjects and selected patient populations, will be required to fully explore the potential of OVAR as an otolith-ocular reflex assessment tool.

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STENTING FOR PEDIATRIC LARYNGOTRACHEAL STENOSIS

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WASHINGTON, DC

The treatment of pediatric laryngotracheal stenosis using open surgery to expand the airway has become a widely accepted and effective method. Stents and cartilage grafts represent the main features of expansion laryngotracheal surgery, which is indicated after failure of endoscopic treatment and/or in the presence of severe stenosis. Stenting is needed in all situations with the exception of using a single cartilage graft in the anterior subglottic lumen. There are several options available for stenting. The most valuable and commonly used stents are the Aboulker stent and the Silastic sheet roll. In looking for the features of an ideal stent, I analyzed 51 procedures using the Aboulker stent on 48 patients. The purpose of this report is to discuss these features and relate them to the Aboulker stent.

KEY WORDS — airway stent, pediatric laryngotracheal stenosis.

Reports advocating or condemning the use of stents in laryngotracheal reconstruction are available. Several kinds of stents have been used. However, two useful stents for pediatric laryngotracheal reconstruction are the Silastic sheet roll and the Aboulker stent. Evans¹ advocated the use of a Silastic sheet (Fig 1A) in a "Swiss roll" manner as a lumen keeper. The roll has a constant tendency to unroll, thus obliterating dead space and allowing mucosal regeneration. A part of the stent is placed in the larynx to keep the vocal cords apart without applying undue pressure on them.

The Aboulker stent (Fig 1B),²⁻⁴ used in the 1960s on both adults and children, proved to be a very effective stent. Grahne,⁵ Cotton and Evans,⁶ and Crysdale⁷ used the Aboulker stent with very good results. Cotton and Evans found that decannulation using the Aboulker stent was much easier than with a Montgomery laryngeal Silastic stent because of less granulation tissue and absence of suprastomal collapse. Crysdale⁷ found that the Aboulker prosthesis was superior to Montgomery T-tubes because of less reaction and secondary granulation tissue formation. A successful outcome (Fig 2) depends on the choice of surgical procedure as a whole rather than the method of stenting. During expansion laryngotracheal surgery, with or without the use of cartilage grafts, stents need to be used in all situations with only one exception: when an anterior cartilage graft is used to repair isolated anterior subglottic stenosis or mild circumferential subglottic stenosis.

Stents are used either to counteract scar tissue formation or to keep the reconstructed segments from falling apart secondary to movement of the laryngo-

tracheal complex during swallowing, coughing, and speech. The duration of stenting is a controversial issue, and the experience of the surgeon usually determines the duration of stenting, depending on certain guidelines. Animal studies (unpublished data) have shown that a minimum period for a posterior cricoid split to heal in a distracted manner when a cartilage graft is inserted is 2 weeks. Removal of the stent before 2 weeks can lead to prolapse of the graft into the lumen. If we want to use a stent to counteract scar contracture, this would theoretically mean stenting for a period of 6 months. The guidelines that determine the duration of stenting depend on the consistency of the stenosis, anatomic distortion, stability of reconstructed areas, and host tissue healing factors (keloid formation).

The Aboulker stent is used in a short form and a long form.⁸ If the short form is used and left in place for 6 weeks or longer, granulation tissue will form at the lower end above the tracheotomy, causing tracheal stenosis and suprastomal collapse. This fact limits the use of these stents to shorter periods of time, and they are indicated in lesions involving the larynx and upper trachea, in which stenting for a short (up to 5 weeks) period is needed. The use of the long form of a stent, in which a metal tracheotomy tube is wired to the stent, is ideal for long-term stenting and for tracheal and tracheostomal lesions. Despite the successful and widespread use of the Aboulker stent, it is far from ideal. The purpose of this report is to discuss the features of an ideal stent and how an Aboulker stent would relate to them.

MATERIALS AND METHODS

Charts and specifically designed data sheets that

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Presented at the International Workshop of Pediatric Laryngotracheal Stenosis, Leeds Castle, Kent, England, July 24-27, 1991.

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Fig 1. Stents. A) "Swiss roll" Silastic sheet. B) Aboulker stent (cigar-shaped) between Montgomery laryngeal stent and T-tube.

are filled at the time of patient evaluation were reviewed. Children treated with laryngotracheal reconstruction using an Aboulker stent at Children's National Medical Center between October 1986 and December 1990 were included. The information collected was studied with emphasis on technical considerations, complications, and outcome.

RESULTS

The Aboulker stent was used in 51 operations on 48

patients (Fig 3). In the 3 patients who needed repeat operations, the Aboulker stent failed. It failed twice in 1 patient, who still remains tracheotomy-dependent. Another patient, with Down syndrome, died of pulmonary complications of respiratory syncytial virus pneumonia. The initial operation on the third patient was a failure secondary to the use of the short form of the Aboulker stent for a period of 3 months with resultant suprastomal and tracheal stenosis. This patient underwent revision surgery using the long

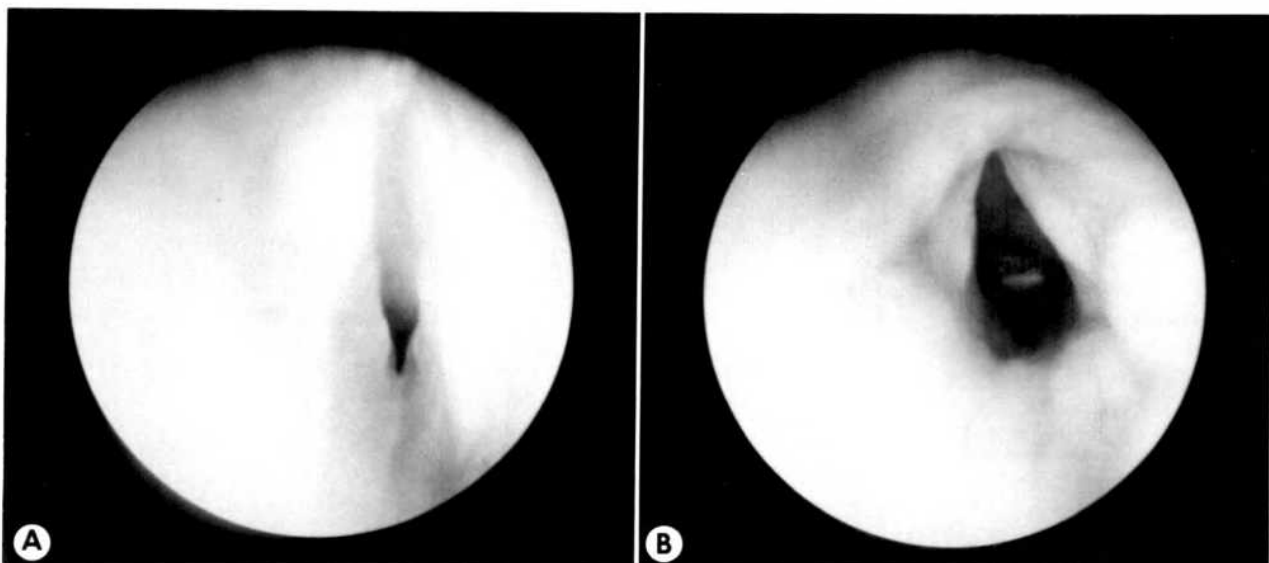


Fig 2. Views of glottic and subglottic areas A) before and B) after reconstruction with anterior and posterior costal cartilage grafts and stenting with Aboulker stent for 4 weeks.

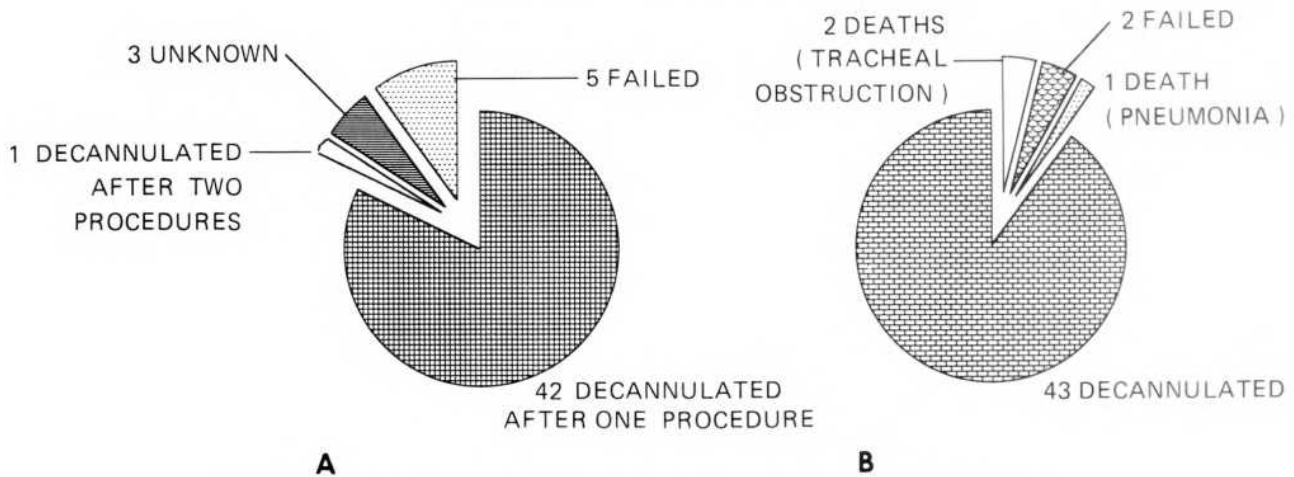


Fig 3. Distribution of outcome. A) By number of procedures. B) By number of patients.

form of the Aboulker stent and is now decannulated.

There were two deaths resulting from tracheotomy obstruction at home. There were no deaths secondary to tracheotomy obstruction when the stent was wired to the tracheotomy. Out of the remaining 45 patients, no further surgery is contemplated on 1 patient (mentioned above), since he is a keloid former and had undergone five open reconstructions before presenting to our institution. There is 1 patient who has a patent airway and can tolerate plugging during the daytime but does not do well at night and still is tracheotomy-dependent during sleep. The rest of the patients (43) have been decannulated and are doing well with follow-up periods of up to 4 years 2 months.

The short form of the Aboulker stent was used five times with only one failure, in a case in which stenting was done for 3 months. The duration of stenting was 3 weeks in the rest of the patients, except for one who underwent stenting for 2 weeks. The usual duration between stent removal and decannulation was around 2 months.

All other patients underwent stenting with the long form of the Aboulker stent, which in general is an indication of a more severe stenosis. The duration of stenting was between 3 and 9 weeks in 28 patients and over 2½ months in the rest. The longest duration was 8 months. Most patients were decannulated between 2 and 3 months after stent removal. The duration between removal of the stent and decannulation may not necessarily reflect any complications or recurrent granulation tissue formation, but can reflect compliance of patients with operating room scheduling, admission to the intermediate intensive care unit, and the protocol we follow for decannulation, which requires a minimum of 6 weeks after removal of the stent.⁹ Most patients underwent two or three endoscopies before they were decannulated.

DISCUSSION

If a surgeon was offered the opportunity to use an ideal stent, the following features would be requested.

It should be available in many sizes. The Aboulker stent exists in many sizes, ranging from a width (outside diameter) of 7 mm to 18 mm, with a length of 120 mm that can be easily shortened. These sizes are appropriate for all situations.

The stent should exist in many shapes to fit reconstructed areas. An ideal shape would be that of the reconstructed lumen — a mold-type stent that can be put in the reconstructed lumen and take its shape. Removal of such a stent should not cause any injuries. The Aboulker stent has a standard cigar shape that cannot be molded or changed. This is a disadvantage, since the largest width of the stent is as big as the narrowest area of the reconstructed lumen. A cigar shape is suitable for the subglottis and trachea and is harmful to the larynx. A stent that would fit in certain segments of the airway without causing damage in other segments is much more preferable.

A stent should be safe, without any risk of obstruction of the respiratory passages. Patients with the long form of the Aboulker stent have a tracheotomy tube wired to the stent. If the tracheotomy tube becomes plugged, it cannot be removed, and this is a potentially lethal complication. All patients are supplied with two inner cannulas that are interchanged during cleaning. An endotracheal tube marked to the length of the tracheotomy tube should accompany the patient at all times, to be used for replacing an inner cannula blocked by a mucous plug that does not dislodge after suctioning. Fortunately, there have been no reported deaths from this method.

The stent should not cause any foreign body reaction. The Aboulker stent is made from highly polished Teflon. However, after placement for a few

weeks — sometimes even a few days — the stent-tracheotomy complex causes mucosal irritation and secondary infection, manifested by a foul-smelling odor that can be controlled with antibiotics. Granulation tissue formation secondary to irritation at the superior or inferior end of the stent and at the tracheotomy site can occur. Erosion at the base of the epiglottis is not uncommon; it usually occurs in patients in whom a stent is placed high in the larynx and is pushing on the base of the epiglottis. However, various degrees of mucosal irritation and secondary formation of granulation tissue have been observed despite adequate placement of the stent. One cause could be posterior displacement of the supraglottic structures, either as a normal finding or because of previous surgery.

Mucosal erosion at the lower tip of the stent depends on whether a short or a long stent has been used. The use of a short stent for a period longer than 5 weeks will ultimately cause granulation tissue formation at the lower end of the stent, above the tracheotomy, secondary to stasis of secretions. The granulation tissue is circumferential and will eventually lead to severe circumferential tracheal stenosis and suprastomal collapse. This can be avoided by using a short stent for a period not to exceed 5 weeks. Granulation tissue formation around the tracheal stoma occurs with the use of metal and nonmetal tracheotomy tubes. However, it is more pronounced in cases in which the tracheotomy tube has been wired to the stent, because of inadequate tracheotomy care secondary to poor access to the skin of that area. Granulation tissue formation at the lower end of a long stent is very rare. In this series, it occurred in three patients, two of them having Down syndrome. The cause, assuming that suctioning and pulmonary toilet are comparable in all patients, may be a mild degree of tracheomalacia leading to erosion of the mucosa secondary to rubbing around the lower tip of the stent. Support for this hypothesis comes from the posterior location of the granulomas, where tracheal support is the weakest. Every effort is always made to polish the lower end of the stent so that it is not sharp. Lower tracheal granulomas are treated with local application of dexamethasone drops and antibiotics. This complication has necessitated removal of the stent in two of the three patients at an earlier date than planned and was instrumental in prohibiting decannulation of one of these two patients. Monthly examination of the lower end of the stent by passing a fiberoptic telescope through the tracheotomy will offer the opportunity of early detection.

A stent should be hard enough to keep reconstructed structures and grafts in place, but soft enough

not to cause discomfort or pressure necrosis of other areas. The Aboulker stent is a hard stent that puts pressure on and possibly damages the mucosa of the edges of the vocal cords. Also, because it is hard, it breaks. (Soft stents may rip.) There were three stents in this series that broke. Since the stent is hard, movement during swallowing, speech, and breathing can lead to erosion through structures and eventual migration. Stent migration occurred in two patients, with complete closure of the supraglottis in one. Monthly laryngeal examination with a fiberoptic telescope will detect any granulation tissue formation or stent migration.

A stent should allow voice production, especially in instances in which stenting may be needed for a long period of time. The Aboulker stent has a hole in its superior end that will allow air escape and voice production. It is easier to produce voice with the short form of the Aboulker stent, because air can flow freely from the suprastomal area through the stent and out of the oral cavity. With the long form air should travel around the tracheotomy inside the stent. The patient can close the tracheotomy with one finger and produce voice. In one patient excessive pressure was needed to allow air to escape through the oral cavity, and neck subcutaneous emphysema developed 6 weeks postoperatively without any sequelae.

A stent should allow easy food intake without aspiration. Because the tip of the Aboulker stent has a hole, placement in a proper location in the larynx is very important. If the stent is placed higher than the level of the arytenoids, aspiration is inevitable. Intermittent aspiration has been a major problem in one patient in whom a short stent was used. Aspiration was intermittently encountered, among short stents more than long stents. If a stent is placed lower than the arytenoids, it may lead to glottic and subglottic granulation tissue.

A stent should allow easy examination and removal. The superior and inferior ends of the Aboulker stent can be easily examined with a rhinolaryngoscope. The items to look for would be mucosal irritation, ulceration, granulation tissue formation, and change in location of the stent. However, the Aboulker stent is not easy to remove. The short form needs a skin incision to release the anchoring suture, and the long form can potentially be complicated by stent breakage and/or complete airway obstruction.

CONCLUSION

The Aboulker stent leaves much to be desired, but is a very useful stent. It has proved itself to be

extremely effective in both counteracting scar contracture and keeping reconstructed areas rigid and in place. The success rate of tracheotomy decannulation with the Aboulker stent has been very high (43 of 45 patients). However, one disturbing aspect of the Aboulker stent has been the apparent but not easy to document damage to the larynx: the Aboulker stent

seems to widen and blunt the anterior commissure and cause pressure damage to the mucosal folds of the vocal cords, thus resulting in poor voice results. The use of external stents^{10,11} may be promising for the treatment of anterior subglottic and tracheal stenosis, laryngeal trauma, and tracheomalacia and after division of complete tracheal rings.

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FIRST EUROPEAN SYMPOSIUM ON PEDIATRIC COCHLEAR IMPLANTATION

The First European Symposium on Pediatric Cochlear Implantation will be held September 24-27, 1992, at University Hospital, Nottingham. For further information, contact the University of Nottingham, Office for Professional and Industrial Training, University Park, Nottingham NG7 2RD, England; telephone: (0602) 792841; fax: (0602) 501718.

PEDIATRIC AIRWAY RECONSTRUCTION AT GREAT ORMOND STREET: A TEN-YEAR REVIEW

III. DECANNULATION AND SUPRASTOMAL COLLAPSE

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One hundred eight consecutive patients with pediatric laryngotracheal stenosis requiring airway reconstruction over a 10-year period were reviewed. Ninety (83%) of the patients were decannulated. Over three quarters of the decannulations took place within 20 months of primary reconstruction. More than half of the patients (47, or 52%) had persistent tracheocutaneous fistulae after decannulation, which required elective closure. The likelihood of a persisting tracheocutaneous fistula is directly related to duration of cannulation.

KEY WORDS — cartilage, intubation, laryngotracheal stenosis, tracheostomy.

INTRODUCTION

The goal of airway reconstruction for pediatric laryngotracheal stenosis is decannulation. The decision as to whether the patient is ready for decannulation is made by serial microscopic laryngoscopy and bronchoscopies after airway reconstruction.

After reconstruction, sometimes the subglottis is wide enough for decannulation but suprastomal collapse obstructs the airway. Suprastomal collapse of the anterior tracheal wall may sometimes be severe enough to prevent decannulation.

In this paper, the issues concerning decannulation and suprastomal collapse after airway reconstruction are addressed.

MATERIALS AND METHODS

A search was undertaken to identify all patients with pediatric laryngotracheal stenosis at The Hospital for Sick Children, Great Ormond Street, who required airway reconstruction from January 1, 1978, to January 1, 1988. These medical records were reviewed in January 1990, so that all patients studied would have a minimum of 2 years of postoperative follow-up.

RESULTS

One hundred eight patients met the above criteria. As outlined in two preceding articles,^{1,2} laryngotracheoplasty and laryngotracheal reconstruction with costal cartilage grafting were used as the methods of

airway reconstruction.

In all, 90 patients (83%) were decannulated. Over three fourths of the patients were decannulated within 20 months after the primary procedure (Fig 1).

As a rule, patients were admitted to the hospital for down-sizing and blocking of the tracheostomy tube prior to decannulation. Six of the patients were noted to have suprastomal collapse on microscopic laryngoscopy and bronchoscopy immediately before decannulation. A total of six patients had surgical decannulation instead of the ward down-sizing protocol (see Discussion); three of these patients had surgical decannulation for suprastomal collapse. Three patients had obstructive tonsils and adenoids that when removed allowed successful decannulation.

Over half of the patients (47, or 52%) developed persistent tracheocutaneous fistulae after decannulation. Patients with persisting tracheocutaneous fistulae tended to have had the tracheostomy for a longer time than those who did not develop fistulae. Patients with fistulae were most often decannulated in the third year, whereas patients who did not develop fistulae were most often decannulated during the first year (Fig 2). Tracheocutaneous fistulae required elective closure under general anesthesia.

DISCUSSION

Decannulation is the goal of airway reconstruction for pediatric laryngotracheal stenosis. Whether a patient is fit for decannulation is a clinical decision

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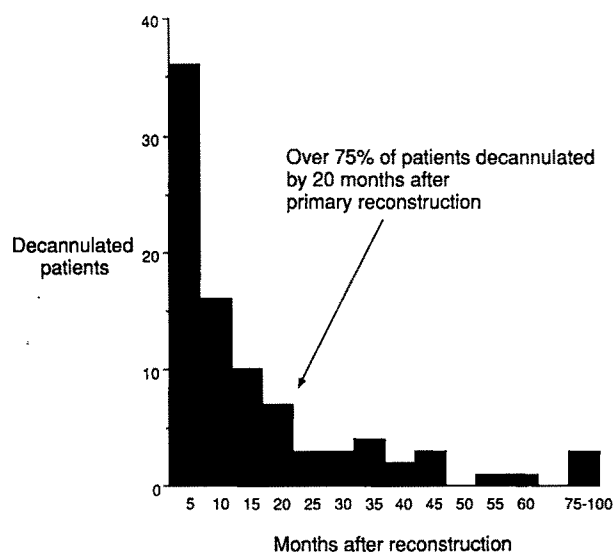


Fig 1. Time elapsed from reconstruction to decannulation. Ninety patients (83%) were decannulated.

based on physical examination of the patient and inspection of the airway. We have found that a helpful rule of thumb is that the patient is ready for decannulation if the subglottic airway admits a bronchoscope that is no more than one size smaller than normal for the patient's age (see Table).

Our ward decannulation protocol has evolved over the years. At present, patients are admitted to the tracheostomy ward and undergo a protocol of down-sizing, blocking, decannulation, and observation. Down-sizing refers to replacing the tracheostomy tube with a tube one size smaller each day until the smallest size (usually 3.0 mm inside diameter) is used. After the smallest tracheostomy tube has been tolerated for 24 hours, the tube is blocked for 12 hours

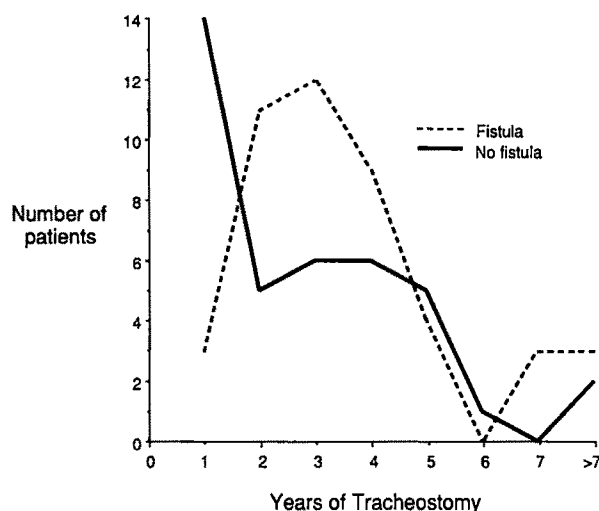


Fig 2. Tracheostomy duration and development of tracheocutaneous fistula. Patients with fistulae were most often decannulated in third postoperative year, whereas patients who did not develop fistulae were most often decannulated during first year.

NORMAL KARL STORZ BRONCHOSCOPE SIZES

Labeled Size (mm Inside Diameter)	True Outside Diameter (mm)	Age Range
2.5	4.0	Premature to neonate
3.0	5.0	Neonate to 6 mo
3.5	5.7	6 to 18 mo
4.0	7.0	18 to 36 mo
5.0	7.8	3 to 8 y
6.0	8.2	>8 y

while the patient is awake during the day and then unblocked at night. If the patient does not suffer respiratory distress, the tube is blocked for a full 24 hours. If no respiratory distress is encountered, the tube is removed the next morning and a loose bandage is applied. The patient remains in the hospital for 7 days after decannulation and is then discharged. Observation of the patient in the hospital for a week after decannulation is necessary, as many of our patients live in remote areas many miles from the closest hospital.

Suprastomal collapse may interfere with decannulation. Patients with suprastomal collapse were concentrated at the end of the study period, as this phenomenon had been recognized only recently and is thus more prevalent in current practice. Although not common overall, suprastomal collapse may be due to the type of stenting used. There is a gap between the Silastic "Swiss roll" and the tracheostomy tube that leaves a portion of the anterior trachea unsupported.³⁻⁵ This area often becomes weakened because of the inward pressure of the tracheostomy tube and therefore collapses into the lumen. Suprastomal collapse may respond to surgical decannulation.

Our method of surgical decannulation in cases of suprastomal collapse now includes "hitching" the collapsed suprastomal trachea forward by suturing it anteriorly to the strap muscles on either side. This provides constant anterior traction on the collapsed area during healing so that the resulting airway diameter is greater. The patient is left intubated postoperatively for at least 48 hours so that the collapsed area of trachea is also supported from within by the tube while the tissues adhere during the early healing phase. Inflammation of the airway is reduced by treatment with 0.25 mg/kg of dexamethasone sodium phosphate intravenously intraoperatively, followed by 0.1 mg/kg dexamethasone at 6-hour intervals for 48 hours postoperatively.

Development of tracheocutaneous fistula after decannulation occurred in about half of our patients with laryngotracheal stenosis. The tracheostomy tract becomes epithelialized, and although it shrinks in diameter after decannulation, it nevertheless persists

permanently. Usually the patient has no difficulty with phonation, as the amount of air escape is small. However, the tracheocutaneous fistula drains mucus that becomes purulent when the patient develops an upper respiratory tract infection, and coughing is less effective. The patient is also restricted from swimming unless an occlusive bandage is worn.

Closure of the tracheocutaneous fistula, if necessary, is the last step in managing patients with laryngotracheal stenosis. After the many general anesthetics for endoscopy required in managing laryngotracheal stenosis, patients' parents are often not eager to subject their child to yet another anesthetic, albeit the last one. We have found that it is often convenient, therefore, to delay elective closure of the fistula until just before the patient enters school. We feel at least 6 months should pass after decannulation to allow an adequate opportunity for spontaneous

closure to occur.

Closure of the fistula involves excising the epithelialized tract and oversewing the tracheal defect, followed by reapproximating the overlying soft tissues and skin. Others⁶ recommend excision of the fistulous tract and temporary replacement of the tracheostomy tube with secondary wound healing to decrease the rate of complications. To date, we have not encountered respiratory obstruction from subcutaneous emphysema from this method of dealing with tracheocutaneous fistulae, despite the large number of our patients with this entity.

Restoring the natural airway and providing an adequate voice are the goals of managing laryngotracheal stenosis. Decannulating patients who previously required a tracheostomy is very rewarding for everyone who cares for these children.

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THE JERUSALEM SYMPOSIUM ON SURGERY OF THE SKULL BASE AND ADJACENT MIDLINE REGION

The Jerusalem Symposium on Surgery of the Skull Base and Adjacent Midline Region will be held March 21-26, 1993, in Jerusalem, Israel. For further information, contact Dr F. Umansky, The Jerusalem Symposium on Surgery of the Skull Base and Adjacent Midline Region, PO Box 50006, Tel Aviv 61500, Israel; Telephone 972 3 5174571; Telex 341171 KENS IL; Fax 972 3 655674.

COMPARISON OF SPEECH RECOGNITION ABILITY WITH DIFFERENT SPEECH PROCESSING STRATEGIES BY KOREAN COCHLEAR IMPLANTEES

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Many variables affect the audiologic performance of cochlear implantees. With current methods of evaluation, it is difficult to directly compare auditory function with different speech coding strategies. We compared the audiologic performance directly with F0F1F2 and multipeak speech coding strategies in the same implanted ear of eight Korean cochlear implantees. We tested word and phoneme recognition abilities using Korean word lists for speech audiometry and two-syllable nonsense words, respectively. With the multipeak coding strategy, a significant difference in discrimination ability was found in the initial fricative consonant phonemes (/s/, /ss/, /h/). Our results suggest that the improvement of speech recognition ability with the multipeak coding strategy comes primarily from the better understanding of the initial fricative consonants.

KEY WORDS — audiologic performance, initial fricative consonants, Korean cochlear implantees, speech coding strategy.

INTRODUCTION

Clinical and experimental experience over the last decade has proved that the cochlear implant is a promising method of rehabilitation for selected profoundly deaf patients who were previously beyond our ability to help. Most researchers are now focusing on the development of new devices to enhance auditory function in profoundly deaf individuals.

Many variables affect the audiologic performance of cochlear implantees, such as speech processing strategies, evaluation methods, and the patient's status (cause and duration of hearing loss, age at implantation, motivation, language development prior to hearing loss, etc).¹⁻⁵ Therefore, the characteristics of audiologic performance by cochlear implantees reported previously showed a wide-ranging variability even with the same implant device.

The current evaluation methods of the efficacy of audiologic performance by cochlear implantees are to compare the patient's auditory function before and after implantation, or to compare overall performance levels of subjects implanted with different devices.^{1,3,4,6,7} By these evaluations, multichannel speech processing strategies were superior at conveying auditory information compared to single-channel cochlear implant designs. In addition, some of the observed variations of performance were related to duration of hearing loss, age at implantation,

motivation, and residual hearing.

Nevertheless, these methods are not able to completely eliminate the variables that affect audiologic performance by cochlear implantees, and therefore it is impossible to directly compare the auditory function efficacy with different speech processing strategies. This study is designed to eliminate most of the above variables and to compare the audiologic performances with two different speech processing strategies (F0F1F2 and multipeak) in the same implanted ear.

MATERIALS AND METHODS

Subjects. Eight of 15 Korean implantees who received auditory rehabilitation for 3 months or more

TABLE 1. SUBJECT HISTORY

Pt No.	Age at Implantation (y)	Causes of Hearing Loss	Duration of Hearing Loss (y)	Residual Hearing
1	36	Sudden SNHL	5	—
2	21	Unknown	21	+
3	70	Ototoxicity	26	+
4	63	Unknown	3	—
5	53	Ototoxicity	18	+
6	24	FUO	9	+
7	41	Ototoxicity	34	+
8	28	Unknown	23	+

SNHL — sensorineural hearing loss, FUO — fever of undetermined origin.

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Presented at the meeting of the Korean Audiological Society, Seoul, Korea, June 2, 1990.

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TABLE 2. FORMANT DISTRIBUTIONS OF KOREAN SIMPLE VOWELS

Vowels	F1	F2	F3	F4	F5	F6
/i/	255 ± 6.0	2,281 ± 25.7	3,106 ± 59.0	4,221 ± 53.2	5,400 ± 0.0	
/e/	488 ± 8.3	1,864 ± 39.6	2,286 ± 52.3	3,519 ± 47.4		
/ä/	633 ± 9.2	1,655 ± 36.9	1,936 ± 35.1	2,646 ± 53.4	3,465 ± 53.0	4,400 ± 0.0
/ö/	481 ± 5.1	464 ± 37.6	2,900 ± 47.0			
/ð/	589 ± 12.5	1,228 ± 36.4	2,309 ± 46.5	3,910 ± 62.5		
/ä/	358 ± 6.7	963 ± 23.0	1,558 ± 31.5	2,238 ± 62.2		
/u/	251 ± 5.8	929 ± 20.8	1,951 ± 41.1			
/o/	484 ± 8.7	928 ± 22.6	1,786 ± 34.9	3,400 ± 67.1		
/a/	770 ± 9.4	1,249 ± 37.8	2,514 ± 60.8	3,437 ± 57.5		

In hertz, for male speaker. Data are mean ± SE.

(range, 3 to 18 months) after implantation of a Nucleus 22-channel device (Cochlear Pty. Limited, Sydney, Australia) were selected (Table 1) by using the following criteria: 1) bilateral profoundly deaf patient showing a positive response to the promontory test, 2) little or no benefit from a hearing aid, 3) post-lingually deaf, 4) 18 years of age or more, 5) psychologically and motivationally suited, and 6) radiologically suited.

Speech Coding Strategies. In the F0F1F2 coding strategy, the first formant is represented by the dominant spectral peak in the range from approximately 300 to 1,000 Hz. The second formant is represented by the dominant spectral peak between 1,000 and 4,000 Hz. In selecting the coding strategy that extracts F0, F1, and F2, the estimate of F1 from the acoustic signal controls the selection of an apical electrode pair, while the estimate of F2 controls the selection of a basal electrode pair. The pulses presented to the two electrode pairs are offset by less than 1 millisecond, so that no interaction can take place between the two quasismultaneous stimulations.

The stimulation rate is determined by the periodicity of the incoming signal. The periodicity detector extracts this information from the voicing or fundamental frequency. For signals that contain little periodicity, such as the voiceless phonemes, a randomized stimulus rate at about 100 pulses per second is generated. Most unvoiced sounds have some periodic component as well, and it is the dominant periodic component for all sounds in the range from 50 to 400 Hz that is used to set stimulation rate.

The multispectral peak coding strategy codes the

F1 (band 1; 300 to 1,000 Hz) and F2 (band 2; 800 to 4,000 Hz) spectral peaks as in the F0F1F2 coding strategy, and in addition, three further bands of spectral information are extracted: band 3 (2,000 to 2,800 Hz), band 4 (2,800 to 4,000 Hz), and band 5 (above 4,000 Hz). The amplitude estimates from bands 3, 4, and 5 are normally presented to the fixed electrodes: electrodes 7, 4, and 1. However, these electrode allocations can be changed.

If the input signal is voiced, F1, F2, and bands 3 and 4 are presented sequentially at the rate of the fundamental frequency (F0). Band 5 is not presented, as there will be negligible information contained in this frequency band. If the input signal is unvoiced, energy in the F1 band (300 to 1,000 Hz) is effectively zero, and this channel has been replaced with a channel presenting information above 4,000 Hz (band 5). The F2 component is presented together with two channels in the frequency range between 2,000 Hz and 4,000 Hz (bands 3 and 4) and one above 4,000 Hz (band 5). The rate of stimulation is higher for unvoiced phonemes and is aperiodic. Differing from the amplitude mapping of the F0F1F2 strategy, the multipeak strategy converts the acoustic signal into a number in the range from 0 to 150 digital units (25 to 1,500 μ A) and has much greater resolution than the F0F1F2 strategy, which codes amplitude into the range of 0 to 31 loudness steps. The multipeak strategy also includes a noise suppression circuit that continually adapts to background noise.

Korean Phonemes. The Korean language consists of 9 monophthongs, 12 diphthongs, and 19 consonants as follows. The Korean vowels include the

TABLE 3. ENERGY DISTRIBUTIONS OF KOREAN FRICATIVE CONSONANTS

Energy	/s/	/ss/	/h/
Noiselike waves unrelated to formants (mean ± SE in Hz)	2,479 ± 197.9 to 8,739 ± 203.3	3,181 ± 127.2 to 9,724 ± 214	Under 1,438 ± 61.0
Peaks of energy	One or two in central or lowest part of noiselike waves	One or two in central or lowest part of noiselike waves	One in central part of noiselike waves
Noiselike waves just before each formant	Absent	Absent	Present

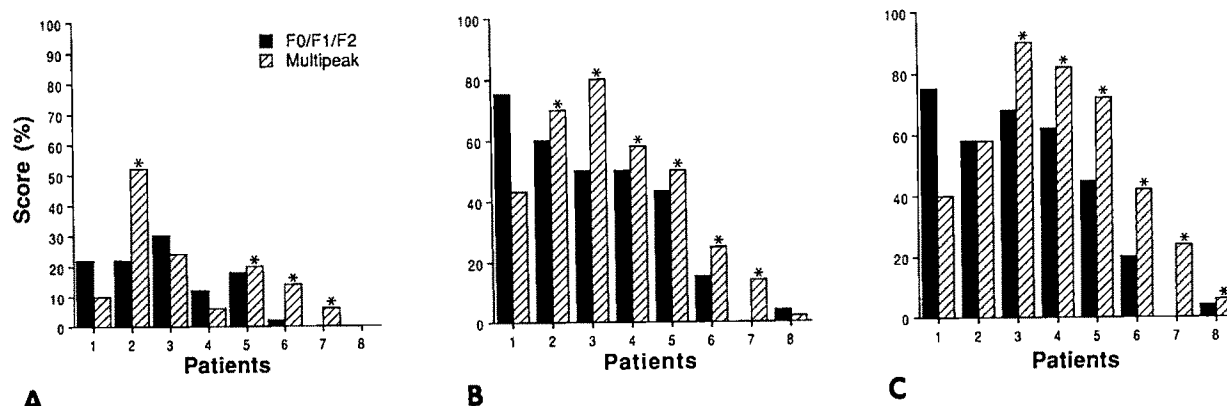


Fig 1. Individual performances on tests of word recognition (open set, sound only). Asterisk — better with multipeak strategy. A) Monosyllable. B) Spondee. C) Trisyllable.

monophthongs /i/, /e/, /ä/, /ö/, /ə/, /ɜ/, /u/, /o/, and /a/ and the diphthongs /ya/, /yɔ/, /yu/, /ye/, /ye/, /wa/, /wə/, /wi/, /we/, /we/, and /wi/.

The Korean consonants include the plosives /k/, /kk/, /kh/, /t/, /tt/, /th/, /p/, /pp/, and /ph/, the fricatives /s/, /ss/, and /h/, the affricatives /c/, /cc/, and /ch/, the nasals /n/, /m/, and /ng/, and the liquid /l/.

The important acoustic cues of Korean simple vowels and diphthongs are the relative frequency distribution and the formant transitions of the first and second formants (F1 and F2), respectively (Table 2). On the other hand, the significant acoustic cues of Korean consonants are the low-frequency noiselike waves just before the first formant in the plosive consonants, the higher-frequency noiselike waves in the fricative consonants (Table 3), the high- and low-frequency noiselike waves in the affricative consonants, and the formantlike low-frequency waves in the nasal and liquid consonants.

Audiologic Assessment. Audiologic performance was evaluated by using two different speech processing strategies (F0F1F2 and multipeak) in the same implanted ear of each patient. All implantees had experience with an F0F1F2 strategy for over 3 months. They switched this strategy to a multipeak one and had 2 weeks of experience with this strategy before the audiologic assessment. A uniform test protocol was applied to the patients, and the battery of tests

consisted of selected items from the Minimal Auditory Capabilities (MAC) test⁸ and tests developed in our own laboratory.⁷

We tested word (monosyllable, spondee, and trisyllable) recognition ability using Korean word lists for speech audiometry. The ability to discriminate Korean phonemes was also analyzed by using two-syllable nonsense words.

All tests were presented to the implantees in the conditions of sound only, vision only, and sound plus vision. The data were analyzed with paired *t* tests by means of the Statistical Packages for Social Sciences on a personal computer.

RESULTS

Word Recognition Ability. The individual audiologic performances on word tests are shown in Fig 1. Some implantees showed a higher performance rate with the multipeak strategy than with the F0F1F2 strategy in the sound-only condition. However, patient 1 had a poorer word recognition score with the multipeak strategy, and half of the implantees (patients 1, 3, 4, and 8) revealed poorer or the same performance on the monosyllable word test.

Average scores on the word tests of eight patients were consistently higher with the multipeak strategy than with the F0F1F2 strategy (monosyllable, 13% ±

TABLE 4. STATISTICAL ANALYSIS OF WORD RECOGNITION

Words	Speech Processing Strategy	N	Mean	SD	t	P
Monosyllable	F0F1F2	8	13.25	11.56	-0.70	.51
	Multipeak	8	16.50	16.34		
Spondee	F0F1F2	8	37.13	27.48	-0.9	.40
	Multipeak	8	42.75	27.30		
Trisyllable	F0F1F2	8	41.50	29.56	-1.39	.21
	Multipeak	8	51.75	29.09		

Paired *t* test.

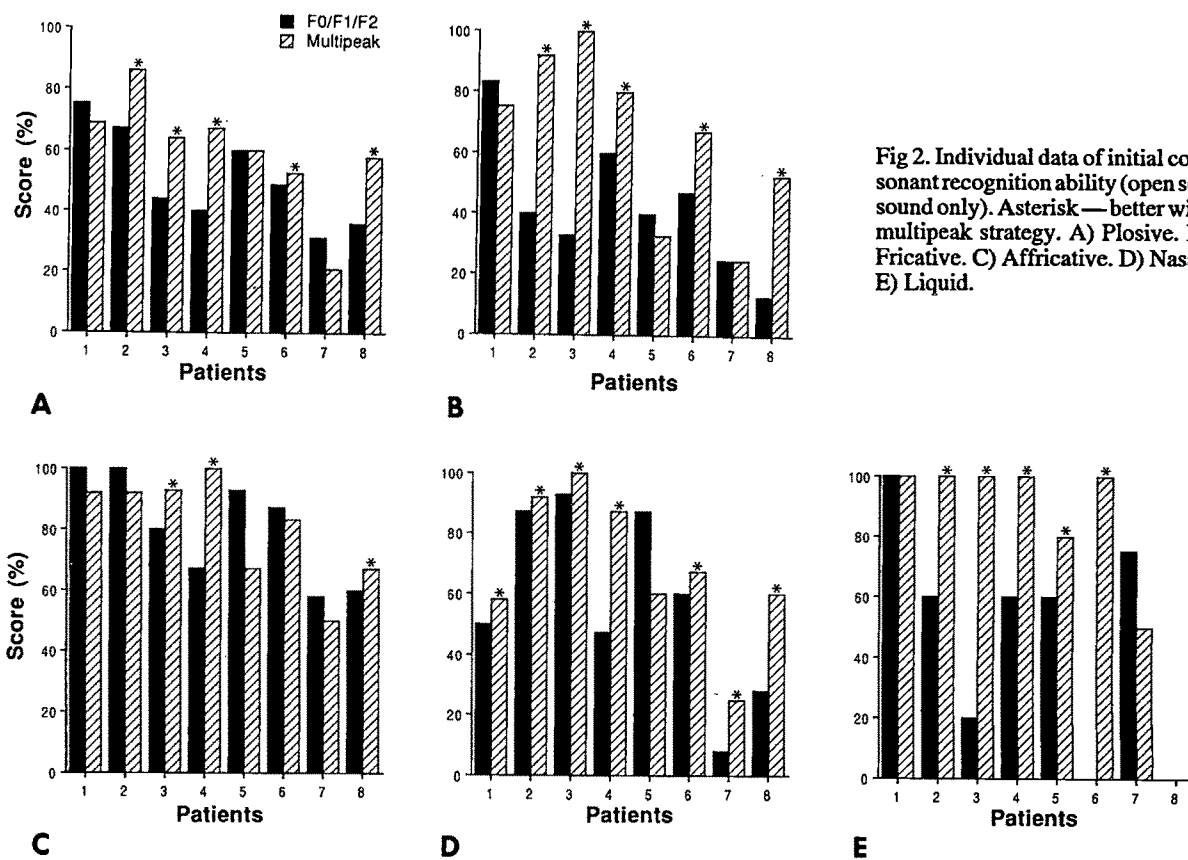


Fig 2. Individual data of initial consonant recognition ability (open set, sound only). Asterisk — better with multipeak strategy. A) Plosive. B) Fricative. C) Affricative. D) Nasal. E) Liquid.

11.9% with F0F1F2 and 17% $\pm$ 16.3% with multipeak; spondee, 37% $\pm$ 27.5% with F0F1F2 and 42% $\pm$ 27.3% with multipeak; trisyllable, 42% $\pm$ 29.6% with F0F1F2 and 52% $\pm$ 29.1% with multipeak). Nevertheless, statistical analysis showed no significant difference between the two groups (Table 4).

In the sound-plus-vision condition, no difference of word recognition ability was found between F0F1F2 and multipeak strategies (monosyllable, 72% $\pm$ 6.0% with F0F1F2 and 76% $\pm$ 9.0% with multipeak; spondee, 97% $\pm$ 4.1% with F0F1F2 and 97% $\pm$ 3.7% with multipeak; trisyllable, 96% $\pm$ 5.0% with F0F1F2 and 98% $\pm$ 3.5% with multipeak).

Phoneme Recognition Ability. Each patient's recognition ability for initial consonants in the sound-only condition is shown in Fig 2. Three of eight implantees (patients 1, 5, and 7) showed poorer or the same performance on plosive and fricative consonant tests. On the other hand, only three implantees (patients 3, 4, and 8) revealed a higher performance rate with the multipeak strategy on the affricative consonant test. Regarding the performance on the nasal and liquid consonant tests, one implantee (patient 5) showed a poorer recognition ability for nasal consonants and three implantees (patients 1, 7, and 8) had poorer or the same performance on liquid consonants

TABLE 5. STATISTICAL ANALYSIS OF INITIAL CONSONANT RECOGNITION

Words	Speech Processing Strategy	N	Mean	SD	t	p
Plosive	F0F1F2	8	50.25	15.61	-1.95	.09
	Multipeak	8	59.87	18.20		
Fricative	F0F1F2	8	46.62	21.53	-2.33	.05
	Multipeak	8	65.62	26.85		
Affricative	F0F1F2	8	80.62	17.18	0.02	.99
	Multipeak	8	80.50	17.32		
Nasal	F0F1F2	8	57.50	30.45	-1.56	.16
	Multipeak	8	68.62	24.01		
Liquid	F0F1F2	8	46.87	36.34	-2.13	.07
	Multipeak	8	78.75	36.42		

Paired t test.

TABLE 6. AVERAGED DISCRIMINATION SCORES OF EACH CONSONANT PHONEME

Consonants		F0F1F2 (N=8)	Multipeak (N=8)
Plosive	/k/	52 ± 23.0	74 ± 33.2
	/kk/	49 ± 23.6	32 ± 25.2
	/kh/	42 ± 23.9	66 ± 36.3
	/t/	60 ± 26.2	71 ± 34.3
	/tt/	43 ± 31.1	51 ± 32.2
	/th/	49 ± 34.9	49 ± 24.0
	/p/	69 ± 26.0	71 ± 24.2
	/pp/	65 ± 29.8	73 ± 21.2
	/ph/	41 ± 27.8	53 ± 27.4
Fricative	/s/	47 ± 34.7	64 ± 39.2
	/ss/	43 ± 28.4	69 ± 29.6
	/h/	38 ± 28.8	64 ± 31.9
Affricative	/c/	71 ± 22.3	83 ± 17.3
	/cc/	95 ± 9.3	81 ± 22.8
	/ch/	76 ± 28.5	78 ± 27.8
Nasal	/n/	46 ± 38.8	57 ± 40.1
	/m/	63 ± 37.7	60 ± 21.5
	/ng/	64 ± 36.1	89 ± 21.0
Liquid	/l/	47 ± 36.3	79 ± 36.4

Data are mean ± 1 SD in percent.

compared to the multipeak strategy.

Average scores on the initial consonant tests of eight patients were higher with the multipeak strategy than with the F0F1F2 strategy, except for the score on the affricative consonant test (Table 5). However, statistical analysis revealed that a significant difference was reached only for fricative consonants (Table 5). Averaged scores for each consonant are shown in Table 6. A significant difference of scores between F0F1F2 and multipeak strategies was found for /k/, /kh/, /s/, /ss/, /h/, /ng/, and /l/. However, we failed to find a significant difference for /kk/, /t/, /tt/, /th/, /p/, /pp/, /c/, /cc/, /ch/, /n/, and /m/ between F0F1F2 and multipeak strategies (60% ± 16.0% with F0F1F2 and 63% ± 15.4% with multipeak).

The individual data of vowel recognition ability are shown in Fig 3. Three implantees (patients 1, 2,

and 8) had poorer or the same discriminating ability with the multipeak strategy. The performance scores of patients 1, 6, and 8 were lower with the multipeak strategy than with the F0F1F2 strategy. Nevertheless, we did not find a significant difference between the two groups (simple vowel, 69% ± 18.8% with F0F1F2 and 67% ± 21.2% with multipeak; diphthong, 63% ± 21.9% with F0F1F2 and 65% ± 29.4% with multipeak).

In the sound-plus-vision condition, the phoneme discriminating ability was not different between F0F1F2 and multipeak strategies (initial consonant, 98% ± 3.8% with F0F1F2 and 95% ± 5.1% with multipeak; final consonant, 99% ± 1.9% with F0F1F2 and 99% ± 2.7% with multipeak; simple vowel, 100% ± 0.6% with F0F1F2 and 100% ± 1.0% with multipeak; diphthong, 99% ± 1.8% with F0F1F2 and 100% ± 0.0% with multipeak).

DISCUSSION

Our intrasubject method of evaluation makes it possible to directly compare auditory function with different speech processing strategies. Our results suggest that the improvement of speech recognition ability with the multipeak coding strategy comes primarily from the better understanding of the initial fricative consonants (Fig 2B and Table 5). In addition, the multipeak coding strategy is also helpful in discriminating Korean initial plosive (/k/, /kh/), nasal (/ng/), and liquid (/l/) consonants (Table 5).

The better understanding of Korean consonants with the multipeak coding strategy may mainly result from the three added basal electrode bands in this strategy, which make it possible to catch other acoustic cues from acoustic energy that is distributed at high frequencies.⁹ However, one implantee (patient 1) had a poor audiologic performance with the multipeak coding strategy. The reason was unclear. This patient had a high threshold level with the bipolar + 1 mode of electrodes, and we modulated his electrode mode to bipolar + 2.

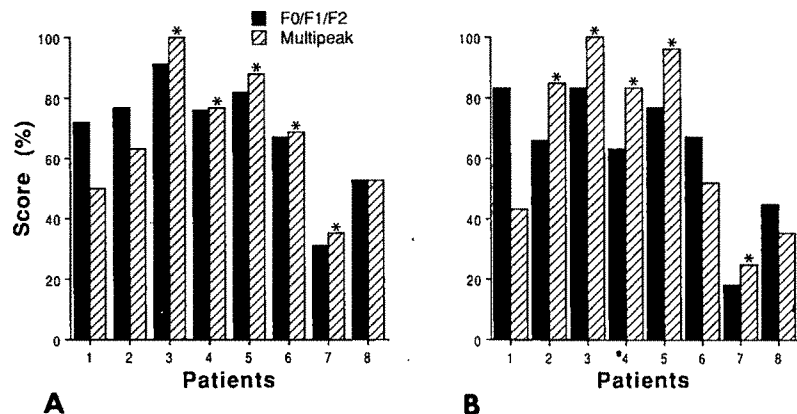


Fig 3. Individual data of vowel recognition ability (open set, sound only). Asterisk — better with multipeak strategy. A) Monophthong. B) Diphthong.

In conclusion, our present results suggest that the continuing development of a speech processing strategy appropriate to the language of each nation is needed to enhance the auditory function of cochlear

implantees, and our results also suggest that different speech coding strategies may be applied to cochlear implantees, depending on their psychophysical responses to electrical stimuli.

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THE UCSF OTOLARYNGOLOGY UPDATE: 1992

The UCSF Otolaryngology Update: 1992, will be held November 5-7, 1992, at the Ritz-Carlton Hotel in San Francisco, California. For more information, contact the University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; telephone: (415) 476-4251.



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The 7th World Congresses for Bronchology & Bronchoesophagology will be held Sept 28-Oct 2, 1992, at the Mayo Clinic and Mayo Medical Center in Rochester, Minnesota. For further information, contact Udaya B. S. Prakash, MD, Secretary-General & Director, 7th WCB & WCBE, East-18, Mayo Clinic, Rochester, MN 55905.

SOLITARY PLASMACYTOMA OF THE SKULL BASE

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Plasmacytomas involving the skull base are rare lesions that may be well advanced by the time of diagnosis. Because of their anatomic site they may produce a variety of signs and symptoms, some of which may be vague, often resulting in delays in presentation and in appropriate investigations. We present such a patient, discuss the diagnosis and management, and give a review of the literature.

KEY WORDS — immunocytochemical staining, plasmacytoma, skull base.

Plasma cell tumors occurring in the head and neck may be solitary or multifocal, and Batsakis¹ classified them in the following manner: 1) a manifestation of multiple myeloma, 2) a manifestation of plasma cell myelomatosis, 3) solitary plasmacytoma of the bone, or 4) extramedullary plasmacytoma (primary plasmacytoma of soft tissues). The incidence of multiple myeloma greatly exceeds that of extramedullary plasma cell tumors,¹ and tumors of this nature localized to the skull base are extremely rare.^{2,3} Although 80% of these tumors are found in the head and neck, they more commonly occur in the nose, paranasal sinuses, nasopharynx, and tonsils.¹

CASE REPORT

The patient, a 64-year-old man, presented with an 18-month history of intermittent horizontal diplopia and a 6-month history of severe right frontal headache. He was assessed at an optometry clinic, where he was fitted with a lens for the right eye, and the diplopia resolved. The headaches, however, became increasingly severe over the ensuing 6 to 8 months and he consulted his general practitioner, who referred him for a neurologic opinion.

On examination, the patient was generally well. His speech, gait, and musculoskeletal systems were normal and there was no loss of weight. His visual fields, fundi, eye movements, and pupillary reactions were normal. No diplopia could be demonstrated. The rest of the cranial nerves were also normal. Findings on indirect nasopharyngoscopy were normal and no cervical lymphadenopathy was noted. The rest of the otolaryngologic, neurologic, and cardiorespiratory examination revealed no abnormality.

Blood tests showed an erythrocyte sedimentation

rate of 12 mm/h and a normal full blood count. The urea, electrolyte, glucose, and liver functions, as well as the results of the *Treponema pallidum* hemagglutination assay, were normal. Serum protein electrophoresis showed increased alpha-1, alpha-2, and beta globulins. Urinalysis was negative for glucose, ketones, and Bence-Jones proteins. A bone marrow aspirate revealed only normal elements.

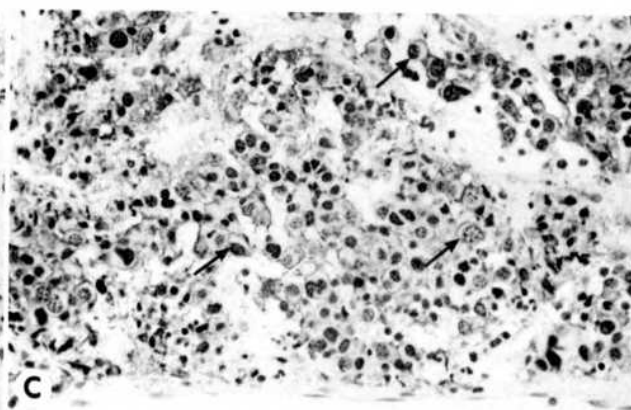
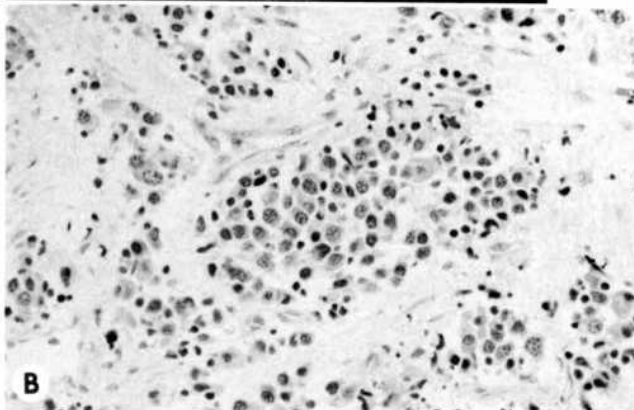
The chest radiograph was normal, but plain skull films showed areas of lucency in the skull base. A computed tomogram of the skull base (see Figure, A) showed a large mass arising from the region of the basisphenoid and extending forward into the sphenoid sinuses and superiorly up through the pituitary fossa to involve the parasellar regions and both the cavernous sinuses. Some extension backward along the tentorial margin on the left was noted, where a large nodule of tissue could be seen projecting toward the left side of the brain stem. Considerable bone destruction was observed. The lesion was predominantly hyperdense, but some enhancement with contrast was noted. A whole body bone scan revealed no other site of bony involvement.

The patient underwent a transsphenoidal biopsy of the mass and made an uneventful recovery. Histologic examination showed a tumor consisting of aggregates of plasma cells separated by thin fibrovascular septa (see Figure, B). Tumor cells were well-differentiated, mature cells with eccentric nuclei and showed the characteristic cartwheel arrangement of nuclear chromatin. There was some degree of nuclear pleomorphism, and a number of cells were binucleated or multinucleated, although mitotic activity was not a feature. No Russell bodies were observed. Methyl green pylonin staining demonstrated strongly pylonophilic cytoplasm in most tumor cells, but Congo

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Solitary plasmacytoma of skull base. A) High-resolution computed tomogram of skull base demonstrating large space-occupying lesion that can be seen projecting posteriorly toward brain stem. B) Photomicrograph of tumor showing aggregates of well-differentiated plasma cells (H & E, original x33). C) Photomicrograph of immunocytochemically stained tumor demonstrating cells with thin rim of cytoplasm positive for L-26 (arrows) specific for B-cell lymphocytes (original x33).



red staining did not reveal any amyloid.

Immunohistochemical techniques were applied by using the following antibodies and the avidin-biotin complex method⁴: cytokeratin, Becton Dickinson desmin, L-26, UCHLI, common leukocyte antibody, and κ and λ light chain (all Dako, United Kingdom). They showed tumor cells reacting positively to antibodies to common leukocyte antigen, L-26, and κ light chain.

The patient was treated by radiotherapy with 44 Gy in 22 fractions and, after 18 months of follow-up, remains symptom-free with no sign of multiple myeloma.

DISCUSSION

The diagnosis of solitary plasmacytoma of bone can never be absolutely certain on the basis of pathologic examination of marrow aspirates, as in-

volvement of marrow may be patchy. It is therefore possible that some patients with an apparently solitary lesion actually have occult multiple myeloma. Patients with solitary lesions on presentation must therefore have lifelong follow-up to detect the manifestations of occult disease. As noted by Woodruff et al,⁵ the very long survival of some individuals with solitary lesions in bone implies that these lesions are indeed solitary.

Extramedullary lesions are more commonly solitary, and three quarters of these lesions occur in patients between 40 and 70 years of age, with a male to female ratio of 4:1. Clarke⁶ has offered a clinical classification of cranial and extracranial plasmacytomas as follows: 1) syndromes of cranial nerve palsy, 2) intracranial tumor syndromes, and 3) intraorbital tumor syndromes.

Clarke has also noted that the most commonly involved cranial nerves are the abducent and the

vestibulocochlear nerves. Clearly, this classification does not allow for small tumors that have not resulted in the development of such syndromes, but which are currently easily visualized by high-resolution tomography and magnetic resonance imaging.

Solitary plasmacytomas are macroscopically variable in appearance, ranging from tannish pink to deep red in color, and may be polypoidal or sessile, becoming lobulated as size increases.¹ Histologically they must be differentiated from plasma cell granulomas and meningiomas with plasma cell infiltrations. Plasmacytomas are virtually monomorphic and only very rarely contain Russell bodies. These are intracytoplasmic accumulations of strongly eosinophilic, periodic acid-Schiff-positive material. These structures are more common in plasma cell aggregates associated with chronic inflammation, and their absence is therefore an important negative observation in the presented case.

Immunocytochemical study with antibodies to κ and λ chains is an important approach to the evaluation of a suspected plasmacytoma.⁷ Monoclonality, as evidenced by a predominant population of cells with cytoplasmic κ or λ chain reactivity, confirms a plasmacytoma. In lesions involving the skull base this is particularly helpful, as local inflammatory responses may otherwise result in errors in diagnosis. This technique has quite clearly demonstrated the nature of the lesion in the presented case (see Figure, C).

Amyloid has been shown to occur in some plasmacytomas, but was not found in the current case. In the 10 cases of solitary intracranial plasmacytoma (SIP) involving the skull base reviewed by Mancardi and Mandybur,⁸ its presence was not reported, and it was noted in only 4 of the 15 recorded cases of SIP involving the meninges or parenchymal nervous tissue. The significance of amyloid in these lesions is unclear, and although it occurs in 20% of solitary plasmacytomas of the respiratory tract,⁹ it does not appear to affect the outcome of intracranial or skull base lesions.¹

None of the 10 skull base SIPs reviewed by Mancardi and Mandybur had been studied immunohistochemically, and only three of the meningeal or parenchymatous lesions,^{8,10,11} including their reported case, were examined by this technique, confirming the monoclonal nature of the lesion.

Toland and Phelps,¹² reporting one of the cases reviewed by Mancardi and Mandybur, have outlined the radiographic features of skull base SIPs. They are usually large and osteolytic and may be one of two varieties: 1) multicystic areas of rarefaction with

sharply defined margins and irregular and sometimes thick trabeculae or 2) destructive, nontrabeculated areas that closely resemble metastatic disease. Despite the above observations, there are no diagnostic radiographic features of these tumors, as the above findings may be produced by other lesions involving the skull base, including chordomas, metastases, nasopharyngeal tumors, eosinophilic granulomas, glomus tumors, meningiomas, and epidermoid tumors. In the presented case, the pattern of destruction most closely resembled that described in the second category, and a preoperative radiologic diagnosis of chordoma was made, emphasizing this point.

It is generally accepted by many authors that precise localization of the primary site may be difficult because of the size of the lesion and the destructive changes present, and this is clearly the situation in the presented case. Toland and Phelps¹² have noted that tumors involving the bones of the skull base only rarely invade the dura and that extension into parenchymal brain has not been seen.

The assessment of the aggressiveness of solitary extramedullary plasmacytomas must be cautious, as the cytoplasmic indices normally used do not correlate with biologic tumor behavior.¹ Bony erosion is a characteristic of more aggressive tumors, and patients who suffer recurrence or persistence of their primary tumor after treatment tend to do worse than those who have no bone destruction. Regional lymphadenopathy does not seem to imply a worse prognosis.

Woodruff et al⁵ have reported their follow-up of 16 patients with extramedullary solitary plasmacytomas involving the head and neck, collected over a 21-year period. Their follow-up periods extended up to 16 years, and 8 patients were followed up for at least 2 years. Patients all received radiotherapy with doses between 25 and 50 Gy. Only 1 patient developed local recurrence, and another developed disseminated disease. They therefore recommend radiotherapy as the treatment of choice and highlight the favorable prognosis in patients with head or neck lesions as opposed to those with plasmacytomas in other sites. Batsakis,¹ however, states that radiosensitivity of such tumors is not a uniform characteristic and points out that there is no clear evidence of superiority of one form of treatment over another. Treatment should therefore be individualized by taking into account locally available facilities as well as the size and site of the tumor and patient factors.

The subtyping of extramedullary plasmacytomas by immunohistochemical techniques and extended follow-up of patients treated by various modalities may allow correlation between tumor types and out-

come once sufficient cases have been analyzed. It is therefore suggested that these techniques should be routinely employed in all tumors of this nature.

SUMMARY

Solitary extramedullary plasmacytomas of the skull

base are a rare clinical entity, and little is known of their biologic behavior. We present a patient with a large lesion of this type involving the skull base who remains well 18 months after treatment with radiotherapy. A review of the diagnosis and management of the condition is discussed.

ACKNOWLEDGMENTS — The authors thank F. Scaravilli, MD, PhD, G. Gould, and Anne White for their help in the preparation of this report.

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FIRST INTERNATIONAL CONFERENCE ON ELECTROCOCHLEOGRAPHY AND MONITORING

The First International Conference on Electrocochleography and Monitoring will be held Sept 20-24, 1992, in Wurzburg, Germany. For further information, contact Program Chairman, Dr. Dirk Hoehmann, Dept of Otolaryngology, University of Wurzburg Medical School, Josef-Schneider-Str 11, D-8700, Wurzburg, Germany; telephone 49-931-201-2323, or fax 49-931-201-2248.

MACROPOROUS BIPHASIC CALCIUM PHOSPHATE EFFICIENCY IN MASTOID CAVITY OBLITERATION: EXPERIMENTAL AND CLINICAL FINDINGS

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Following our previous experimental studies on the performance of macroporous biphasic calcium phosphate (MBCP) in canine mastoid cavities, we used this material in patients requiring surgical intervention. Twenty-two cases were selected, and in eight specific cases a biopsy specimen was taken. Histologic, ultrastructural, and microanalysis studies were performed. This study demonstrates the effectiveness of MBCP implants as bone graft substitutes for mastoid cavity obliteration. Clinical evaluation of the series and histologic and ultrastructural results demonstrated the bioactivity and osteoconduction of this material, with partial transformation of MBCP granules into lamellar bone after several months.

KEY WORDS — biomaterial, calcium phosphate, ceramic, mastoid cavity obliteration, otologic surgery, tympanoplasty.

INTRODUCTION

In otologic surgery, cavities formed after radical mastoidectomy may suppurate; hence, they need regular attention for as long as the patient lives. Owing to its depth, the cavity is difficult to treat and can constitute a source of recurrent infection. The absence of the posterior wall of the external auditory canal (EAC) makes it difficult to rehabilitate hearing surgically.

Numerous techniques have been introduced to deal surgically with these cavities, but they have not proved to be entirely satisfactory. Ceramics have been proposed for bone filling, in particular calcium phosphates used in order to provoke a reaction of osteogenesis.¹⁻³

The calcium phosphate ceramics, otherwise known as hydroxyapatite (HA) and β -tricalcium phosphate (β -TCP), have been extensively researched as bone substitutes in bone repair.⁴⁻⁸ These calcium phosphate ceramics, regardless of composition (HA or β -TCP), have been shown to be compatible^{9,10} and to be able to bond tightly with the host bone.^{7,8,11-13}

Bearing in mind the performance of macroporous biphasic calcium phosphates (MBCP) in orthopedic surgery^{7,8} and considering the chemical and biologic properties of MBCP, we decided to test MBCP granules in the filling of the canine mastoid. We then transferred this technique to humans, starting in 1986.¹⁴ The aim of this paper is to report on the results

from studies on animals and compare them with the clinical, histologic, and ultrastructural results in 22 humans.

MATERIALS AND METHODS

We used 0.5- to 1-mm MBCP granules consisting of 60% HA and 40% β -TCP (Triosite, Xomed-Zimmer) and presenting both macropores (400 to 600 μ m) and micropores (5 μ m). For both animals and humans, the MBCP granules were mixed (1:1) with fibrin glue (Tisseel Immuno) just before filling the cavity. The fibrin glue was prepared with a low concentration of thrombin (4 μ L/mL) for slow setting. The mixture, forming a kind of plastic bone cement, was placed in the cavity in small quantities and carefully compacted to prevent the formation of dead spaces.

ANIMAL EXPERIMENT

We carried out a bilateral mastoidectomy on seven mongrel dogs with healthy ears. The posterior wall of the external auditory canal was preserved. On the right, we implanted MBCP granules alone, and on the left, granules mixed with fibrin glue. The dogs were painlessly killed at 6 months and 1 year. Then the petrous bone was removed and fixed.

CLINICAL STUDY

We implanted MBCP granules in 22 patients selected for obliteration of mastoidectomy cavities, including 13 men and 9 women whose average age

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was 29 (16 to 56 years). Eight patients underwent a radical mastoidectomy for excision of a cholesteatoma with immediate reconstruction, while the 14 others had previously undergone a radical mastoidectomy that had to be reoperated owing to complications.

TECHNIQUE

As a first step, we gently elevated the skin of the posterior wall or of the mastoid cavity. After excision of any existing cholesteatoma, we carefully drilled until healthy bone capable of stimulating osteogenesis was reached. We then filled the cavity with MBCP granules mixed with fibrin glue (1 g Triosite and 1 mL Tisseel). We reformed either antro-attical or antro-attico-mastoidal defects, depending on the cavities. Then a large piece of temporal fascia was applied over the entire area. Tympanoplasty was performed with a second fascia graft by an underlay technique. Finally, ossicular reconstruction was performed simultaneously or several weeks later.

At the time of the revision for eight patients, 8 to 12 months later, we were able to carry out biopsies of the areas that had been filled. It was necessary to use a hammer and chisel to extract block specimens.

HISTOLOGIC, ULTRASTRUCTURAL ANALYSIS AND ELECTRON MICROPROBE

A fragment of human implant sample was fixed in Bouin's solution for decalcified histologic analysis. Other fragments were fixed in a glutaraldehyde solution and embedded in methylmethacrylate. Undecalcified samples were cut into 60- to 100- μ m thick sections with a diamond saw and studied by using polarized light microscopy and microradiography

performed at 15 kV. Some sections were coated with carbon and studied by scanning electron microscopy. A microanalysis was also carried out on the same sections with an EDAX 9100/60 dispersive energy electron microprobe.

Small blocks of implant specimens were fixed for 2 hours in glutaraldehyde, followed by 1 hour in osmic acid, and then embedded in butyl-methylmethacrylate without prior decalcification. Ultrathin sections were cut with a diamond knife and observed by high-resolution transmission electron microscopy using a Temscan JEOL 200 CX operating at 200 kV.

RESULTS

CLINICAL RESULTS

In all dogs (N=7), whatever the date of experimental sacrifice, the tolerance of the biomaterial was excellent, and no inflammatory reaction was observed. In humans (N=22), we lost track of one patient, and the average observation span for the other patients of this series was 15 months (6 to 33 months). The skin of the posterior wall directly in contact with the granules presented a normal aspect in 54% of the cases after 2 weeks and in 96% after 1 month. At 3 months, the skin presented a normal aspect and thickness, and it never changed, as shown by our patients followed up over a 2.5-year period. All the ears operated on remained dry long after operation, even if the operation was for an immediate reconstruction after an open technique, or for the obliteration of a former mastoidectomy cavity. In 10 cases (40%) we observed a serous discharge in the ear canal lasting 3 weeks on average, with migration of some granules, which can be related to an insufficient coverage by the fascia.

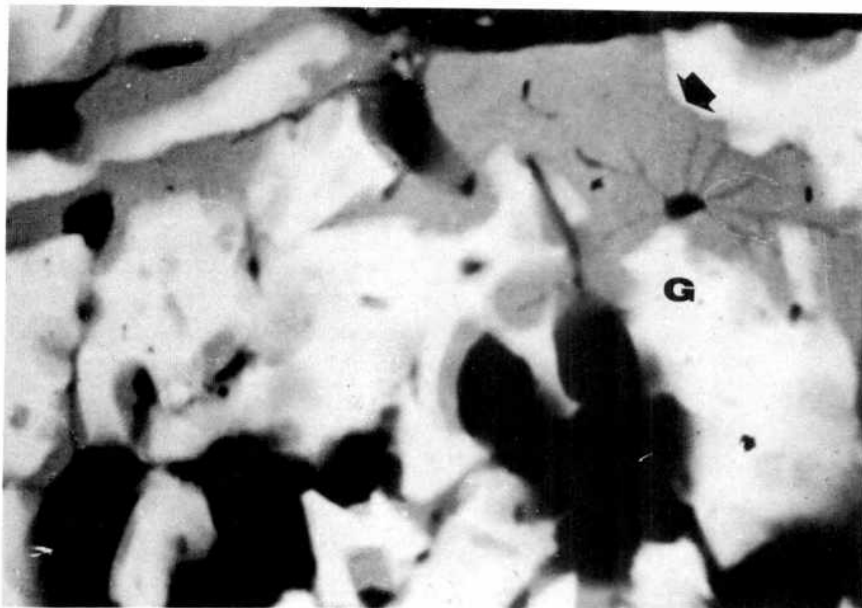


Fig 1. X-ray radiography of macroporous biphasic calcium phosphate granules (G) implanted in dog for 9 months revealing newly mineralized bone formation (arrow; original x20).

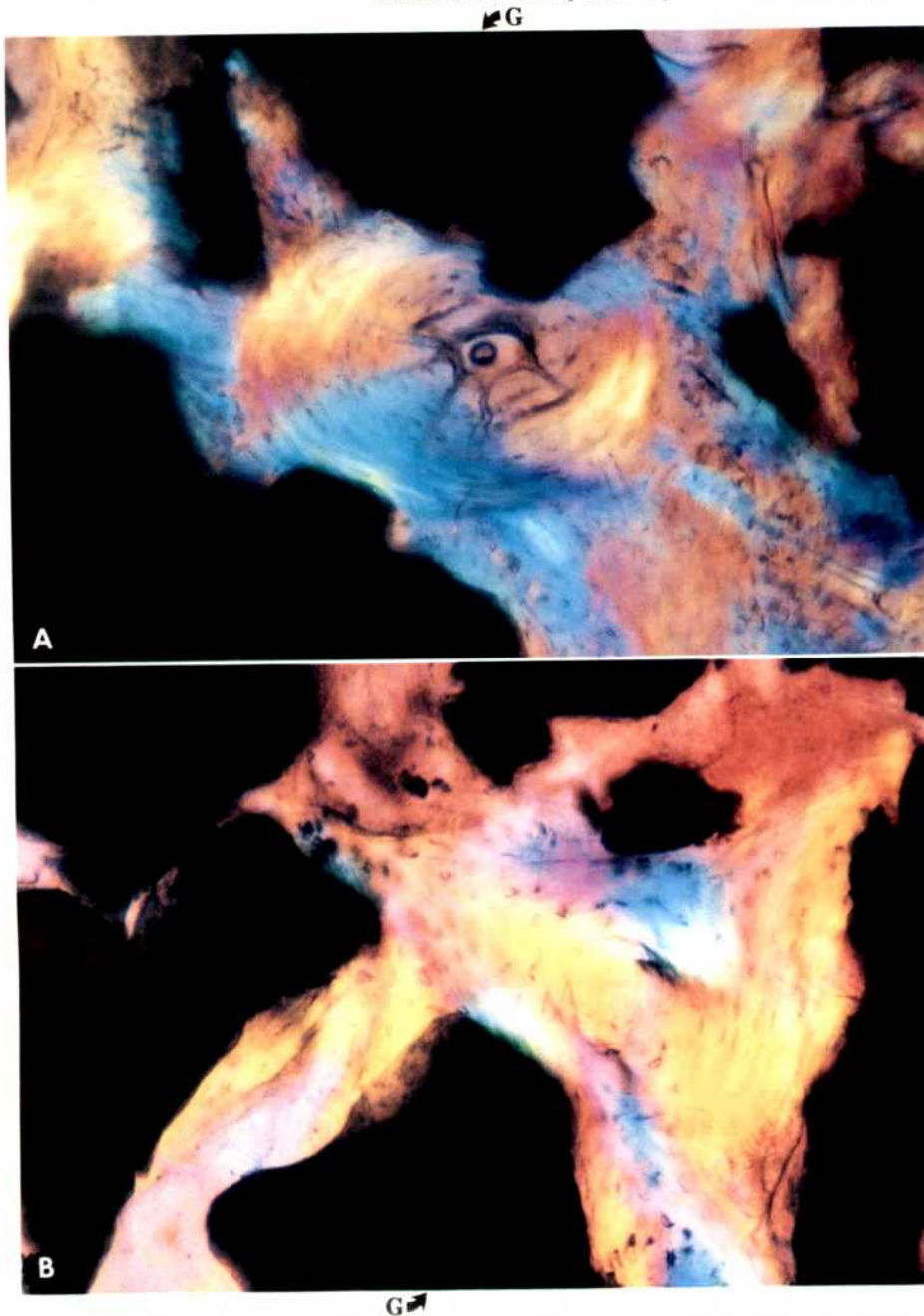


Fig 2. Polarized light microscopy of nondecalcified sections (original x40). A) Haversian bone formation in close contact with MBCP granules (G) in dog. B) MBCP granules (G) implanted for 1 year in human.

Three patients presented a local postoperative infection with purulent discharge and granule migration that responded quickly to treatment. When a migration of granules occurred, it led to a partial resorption of one fourth of the filled volume at most and did not affect the quality of the clinical results.

HISTOLOGIC RESULTS

Animals. The granules implanted in canine mastoids showed bone formation covering the implant and were in close contact with the MBCP. The analysis in polarized light revealed lamellar-type bone structures usually associated with MBCP granules. After 9 months the reduction in size of the granules was around 25%, indicating that a partial

resorption of the calcium phosphate ceramic had taken place.

Microradiography showed that the newly formed bone was well mineralized and had started to form at the surface of the MBCP (Fig 1). In the left mineralized bone (Triosite and Tisseel), we observed in places the existence of new well-vascularized haversian-type bone (Fig 2A), which confirmed the remodeling process. Scanning electron microscopy also confirmed that the macropores had been invaded by lamellar bone formations in close contact with the surface of the MBCP, although without a fibrous interface (Fig 3).

An electron microprobe study of MBCP particles



Fig 3. Scanning electron microscopy of polished section of MBCP granules after 9 months of implantation in dog (original x150).

after implantation revealed an increase in the calcium-phosphorus ratio, although there was the same ratio between the adjacent bone and the newly formed bone in contact with the granules (see Table). Transmission electron microscopy of the interface between the newly formed bone and the granules revealed the presence of a mineralized collagenic network similar to that of the implanted bone and in close contact with the ceramic crystals (Fig 4A). High-resolution transmission electron microscopy of micropores (inter-crystalline spaces) showed new needle-shaped crystal formations, similar to those observed in bone tissue, filling all the spaces between the MBCP crystals (Fig 4B).

Humans. For the first time in humans, it was possible to observe osteogenesis promoted in a mastoid by an MBCP ceramic. The results were comparable to those observed in dogs. When specimens were removed, the uppermost granules of the filling material in the mastoid seemed more or less covered by a smooth, milky white, very dense bone formation. That it was necessary to use a hammer and chisel shows how solid the new bone had become.

Microscopy showed the presence of a mineralized bone formation all around the granules and in the macropores. Haversian-type lamellar bone appeared in the intergranular spaces (Fig 2B). Transmission electron microscopy of the bone-granule interface revealed a mineralized bone matrix in close contact with the MBCP crystals (Fig 4C). Microradiography and microanalysis produced results identical to those

ELECTRON MICROPROBE ANALYSIS OF
MBCP GRANULES BEFORE AND AFTER
IMPLANTATION, AND COMPARING NEWLY
FORMING BONE AND HOST BONE

	MBCP		New Bone	Host Bone
	Before Implanta- tion	After Implanta- tion		
Calcium- phosphorus ratio	2.00	2.20	2.08	2.34
(weight ratio)	± 0.10	± 0.10	± 0.10	± 0.10
MBCP — macroporous biphasic calcium phosphate.				

obtained in animal studies.

DISCUSSION

The calcium phosphate ceramics HA and β -TCP are used clinically for bone reconstruction in periodontal, orthopedic, and maxillofacial surgery.⁴⁻⁸ Biphasic calcium phosphate ceramic, being a mixture of HA and β -TCP, is resorbable to a degree that is a function of the HA to β -TCP ratio.¹⁵ An animal study showed that the biologic performance of MBCP ceramics improved when they were used in connection with repair of defects due to bone loss.¹⁶ Previous studies in which we used noncommercial MBCP, consisting of HA- β -TCP in various proportions, confirmed that the mixture of an equal amount of HA and β -TCP was particularly effective.¹⁵ This explains why, in both the experiments on animals and in this clinical study, macroporous granules consisting of 60% HA and 40% β -TCP were used.

The histologic results revealed bioactivity and osteoconduction in MBCP ceramics. The granules became smaller with time; hence, resorption was taking place according to the degree of β -TCP bioactivity and the stability of the HA. Following the biodegradation and healing of the implanted site, the osteoblasts of the bone that received an implant invaded the macropores and the spaces between the MBCP granules. True bone—characterized by osteocytes, a mineralized bone matrix, and, because of remodeling, a haversian-type system—appeared between the pores.

We observed that in general the newly formed bone appeared first on the surface area of the MBCP granules and that it was made up mainly of lamellar bone and “scarcely woven” bone. In other human applications (spine fusion, long bone filling) we have noticed the same results.^{7,8} According to our previous studies, it seems that 2 or 3 months are needed before the new bone starts to look like normal bone.¹⁷

In the series, the three cases that presented a local infection also showed a certain degree of resorption

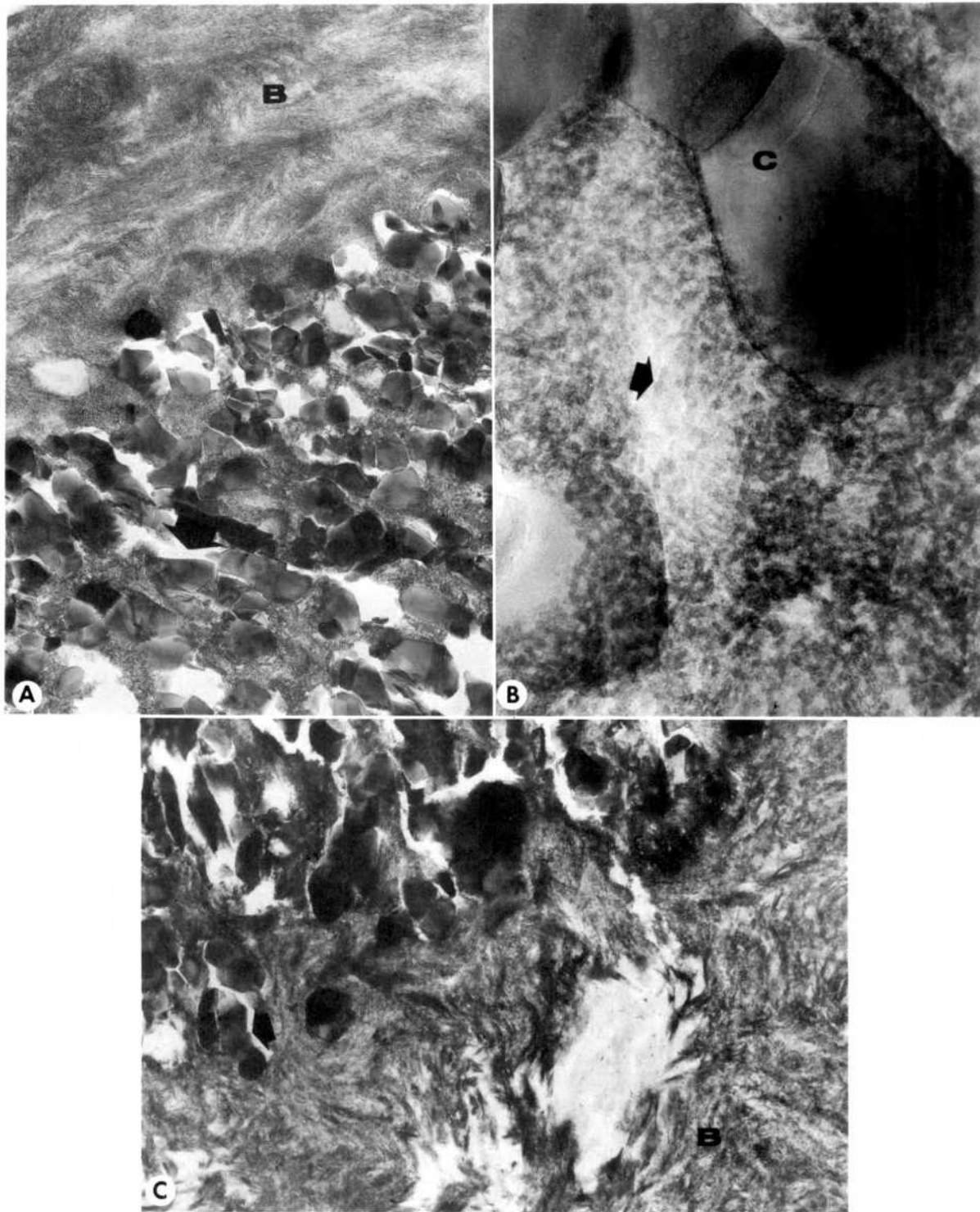


Fig 4. Transmission electron microscopy. A) Mineralized bone interface (B) with MBCP crystals (arrow) in implanted dog (original x20,000). B) Higher magnification of newly formed apatite crystals (arrow) inside spaces (micropores) between MBCP crystals (C) in dog (original x150,000). C) Mineralized bone interface (B) with MBCP crystals (arrow) in human MBCP implantation (original x20,000).

of the granules, but it never compromised the functional results of the bone reconstruction. The various processes of osteogenesis, after being impeded for a short time by the inflammatory reaction secondary to the infection, took their normal course after the

ear became dry. In the case of the mastoid, because of the thickness of the filling and the relatively poor vascularization of the mastoid bone, it is easy to understand the absence of new bone formation deep in the core of the filled cavity after only 8 to

10 months, but cohesion was sufficient to ensure the stability of the filling material and attain the quality we sought. Strict monitoring during the first weeks is absolutely necessary to guide healing by means of local treatment. The skin of the external auditory meatus tolerates contact with the granules very well. Fibrin glue used in conjunction with the MBCP granules makes the implanting stage easier while ensuring the cohesion of the granules and providing greater stability all around.

CONCLUSION

The use of MBCP for the filling of the mastoid in obliteration of mastoidectomy cavities produces stable newly formed bone tissue. The fact that the material

is widely available and easy to handle when used in conjunction with fibrin glue permits its use in all mastoid cavities. The effectiveness of the mixture with a biphasic ratio of 60% HA and 40% β -TCP seems to be confirmed by histologic results obtained in animals and humans alike.

In this 22-case series, the time span has not yet been long enough to allow comment on long-term results. However, among all the proposed techniques for obliteration of mastoidectomy cavities, the use of MBCP for the filling of the mastoid is of great interest, mainly because the material is widely available, thus saving time. Filling the mastoid cavity with a mixture of MBCP granules and fibrin glue seems to be a convenient procedure for mastoid obliteration.

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EDITOR'S NOTE

We almost never make editorial comment on a particular paper, but in this case we feel we should. Daculsi et al have made a fine case for their particular cavity obliteration procedure, and have done an excellent basic research study of its outcome in animals.

Lacking, however, is the sine qua non in the text of any proof of efficacy over open cavity mastoidectomy, ie, control of the cholesteatoma for which the operation is performed.

This can only be considered, then, a preliminary report. We look forward to a follow-up report to learn how recurrences were monitored for and handled.

AIRFLOW STUDY OF PATHOLOGIC LARYNGES USING A CONSTANT TEMPERATURE ANEMOMETER: FURTHER EXPERIENCE

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Phonatory airflow was recorded in 361 laryngeal disease patients and 59 normal subjects by using a constant temperature anemometer to measure Isshiki's proposed parameter, the AC/DC percentage. The pathologic groups displayed AC/DC percentage values smaller than those of the normal group. The value differentials observed among the various diseases suggest that the AC/DC percentage may reflect the vibrational capacity of the vocal cords.

KEY WORDS — vocal cord vibration, voice function test.

INTRODUCTION

Phonation into a constant temperature anemometer yields a waveform characterized by a series of quasitriangular shapes. This airflow pattern results from the opening and closing movements of the vocal cords during vibration. A reduction in the highs of these triangular shapes (AC component) is seen in many laryngeal diseases and is due to the increased leakage of air caused by the vocal cords' reduced capacity for vibration. Isshiki¹ proposed that the vibrational capacity of the vocal cords in various pathologic conditions can be expressed by means of the AC/DC percentage, in which AC represents the effective values calculated from the AC component and DC represents the mean airflow rate during sustained phonation. This hypothesis was substantiated in a subsequent study by Kitajima.² The present study retested the clinical usefulness of the AC/DC percentage with a large sample of laryngeal diseases.

Figure 1 is a simplified presentation of the airflow waveform during sustained phonation. The vertical axes represent the airflow rate (volume velocity). In the normal larynx, shown in the upper diagram, the airflow rate registers zero at the moment of complete glottal closure; in the pathologic larynx (bottom diagram) this does not occur because of the constant leakage of air through the glottis. The AC values are therefore smaller in the latter case, resulting in a lower AC/DC percentage when the DC (mean airflow rate) components are the same.

Figure 2 shows samples of four actual airflow curves, one normal and three pathologic. The top left example is from a normal larynx, the bottom left sample is from a case of unilateral vocal cord palsy, the top right sample is from a case of polyps, and the

bottom right sample is from a case of laryngeal cancer (T1). The AC/DC percentages are 60%, 9%, 29%, and 38%, respectively.

MATERIALS AND METHODS

Three hundred sixty-one patients (see Table) with various pathologic conditions of the larynx were selected for this study. Clinical diagnoses were reached on the basis of indirect laryngoscopy, fiberoscopy, and, in some patients, histopathologic examination. The Table lists the 12 pathologic conditions considered. The control group consisted of 31 men and 28 women free from laryngeal and pulmonary diseases.

Measurements were carried out with the Phonation Analyzer (PA-500), manufactured by the Minato Medical Science Company, Ltd, Osaka, Japan. The subjects were asked to phonate at a comfortable pitch and intensity into a cylindric mouthpiece of the device; the analyzer was designed to show the DC

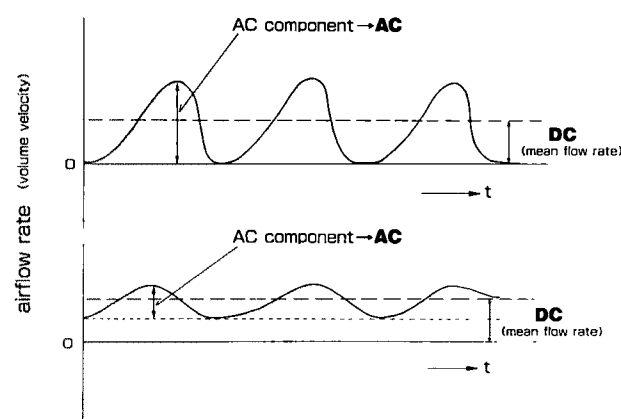


Fig 1. Schematic drawings of airflow waveforms during sustained phonation by normal (upper) and pathologic (lower) larynges.

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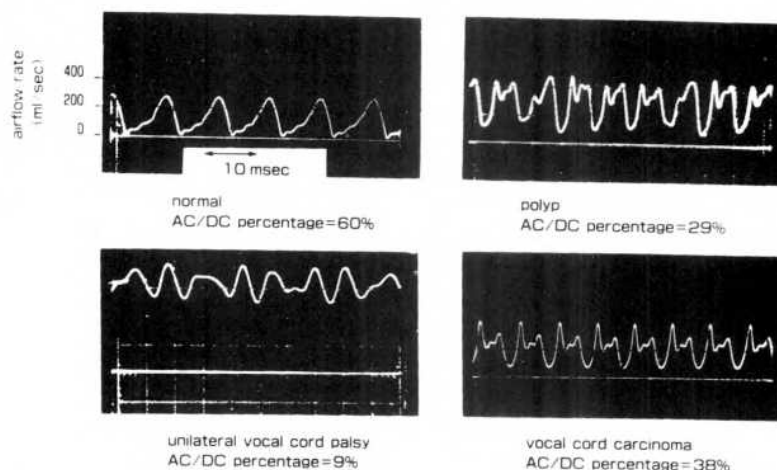


Fig 2. Four examples of real recordings of airflow waveform.

component and the AC/DC percentage as digital values.

Since the goal of the present study was not the performance of differential diagnosis based on the AC/DC percentages but the determination of whether meaningful percentage differences could be found among the various pathologic conditions, *t* test results were used in a comparison of the mean AC/DC percentage values for each disease. The DC values were also compared among the various conditions.

RESULTS AND DISCUSSION

Figure 3 presents an analysis of the average AC/DC percentages obtained in this study. The conditions studied, including both the normal condition and the various disorders, are listed along the top of the chart, and again in the same order along the right side. The diagonal row of blocks from the top left to the bottom right, formed where the horizontal and vertical columns for the same conditions meet, shows the AC/DC percentages and — beneath them in

parentheses — the standard deviations. The asterisks in the chart indicate the existence of a statistically significant difference (*t* test $p < .01$) in the AC/DC percentage between two different conditions. For example, T1 vocal cord carcinoma (highlighted on the chart with a shadow band) shows significantly different values from acute laryngitis, T2 vocal cord carcinoma, T3 vocal cord carcinoma, unilateral vocal cord palsy, and the normal larynx. Figure 4 lists the average DC values in the same manner.

Patient Group Versus Normal Group. Eleven of the 12 disorders showed a smaller mean AC/DC percentage than the normal group (Fig 3), while 8 of the 12 disorders showed larger than normal DC values (Fig 4). Except in the case of chronic laryngitis, these latter 8 disorders also displayed smaller than normal AC/DC percentages. This finding points to an initial effect by the AC component on the percentage, furthered by a subsequent effect of the DC component; ie, the AC/DC percentage was not altered by inadequate glottal closure alone, but necessitated a certain decrease in the value of the AC component. The pathologic conditions that displayed smaller than normal AC/DC percentages in association with normal DC values were T1 cancer, dysplasia, granuloma, and spasmodic dysphonia.

Differences Among Pathologic Conditions. The AC/DC percentage (Fig 3) of unilateral vocal cord palsy was different from those of 6 of the other 11 disorders considered; percentages in acute and chronic laryngitis and vocal cord nodules differed from those of 5 of the disorders; percentages in polyps and T1 and T2 carcinoma differed from those of 4 disorders; percentages in T3 carcinoma and polypoid vocal cord differed from those of 3 disorders; the percentage in vocal cord dysplasia from that of 1 disorder; and the percentages in spasmodic dysphonia and granuloma from those of no disorders.

The DC values (Fig 4) of unilateral vocal cord

NUMBERS OF SUBJECTS FOR EACH TYPE OF PATHOLOGIC CONDITION TESTED

Pathologic Condition	Men	Women	Total
Polypoid vocal cords	21	21	42
Polyp	39	24	63
Vocal cord nodules	2	37	39
Contact granuloma	3	4	7
Chronic laryngitis	15	5	20
Acute laryngitis	11	23	34
Vocal cord dysplasia	10	1	11
Vocal cord carcinoma			
T1	30	0	30
T2	16	0	16
T3	29	0	29
Spasmodic dysphonia	0	7	7
Unilateral vocal cord palsy	37	26	63
Total			361
Normal control	31	28	59

polypoid vocal cords	polyp	vocal cord nodules	contact granuloma	chronic laryngitis	acute laryngitis	vocal cord dysplasia	vocal cord carcinoma T ₁	vocal cord carcinoma T ₂	vocal cord carcinoma T ₃	spasmodic dysphonia	unilateral vocal cord palsy	normal	
38.3 (15.2)					*			*			*	*	polypoid vocal cords
	34.3 (15.1)	*		*	*						*	*	polyp
		42.8 (15.2)			*			*	*		*	*	vocal cord nodules
			31.7 (18.3)									*	contact granuloma
				47.3 (15.8)	*			*	*		*		chronic laryngitis
					24.9 (14.5)		*					*	acute laryngitis
						37.0 (12.8)					*	*	vocal cord dysplasia
							42.2 (17.3)	*	*		*	*	vocal cord carcinoma T ₁
								25.4 (15.6)				*	vocal cord carcinoma T ₂
									28.4 (15.9)			*	vocal cord carcinoma T ₃
										30.6 (15.9)		*	spasmodic dysphonia
											20.7 (13.1)	*	unilateral vocal cord palsy
												55.1 (10.6)	normal

Fig 3. Analysis of average AC/DC percentages obtained in this study. Conditions studied, including both normal and those of various disorders, are listed along top of chart, and again in same order along right side. Diagonal row of blocks from top left to bottom right, formed where horizontal and vertical columns for same conditions meet, shows AC/DC percentages and — beneath them in parentheses — standard deviations. Asterisks indicate existence of statistically significant difference (t test $p < .01$) in AC/DC percentage between two different conditions.

palsy differed from those of all other types of disease. The remaining conditions showed far lower levels of difference in DC with regard to the other disorders:

T2 cancer differed from three disorders, spasmodic dysphonia and granuloma differed from two, and the remainder differed from one.

polypoid vocal cords	polyp	vocal cord nodules	contact granuloma	chronic laryngitis	acute laryngitis	vocal cord dysplasia	vocal cord carcinoma T ₁	vocal cord carcinoma T ₂	vocal cord carcinoma T ₃	spasmodic dysphonia	unilateral vocal cord palsy	normal	
199.1 (85.8)											*	*	polypoid vocal cords
	174.7 (68.3)										*	*	polyp
		183.8 (96.9)									*	*	vocal cord nodules
			109.7 (68.7)				*				*		contact granuloma
				196.2 (106.2)							*	*	chronic laryngitis
					195.9 (94.0)						*	*	acute laryngitis
						177.4 (56.6)					*		vocal cord dysplasia
							166.9 (75.4)				*		vocal cord carcinoma T ₁
								219.9 (69.7)		*	*	*	vocal cord carcinoma T ₂
									200.7 (137.4)		*	*	vocal cord carcinoma T ₃
										116.9 (34.9)	*		spasmodic dysphonia
											413.2 (244.2)	*	unilateral vocal cord palsy
												139.9 (66.0)	normal

Fig 4. DC values averaged for each type of disorder and normal conditions, listed in same manner as in Fig 3.

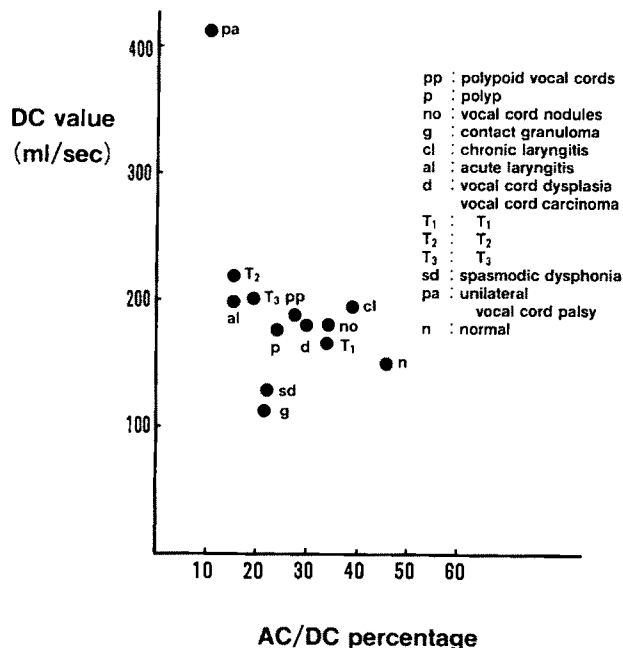


Fig 5. Each type of disorder listed in Figs 3 and 4 is plotted with AC/DC percentage as abscissa against DC value on ordinate.

Correlation Between AC/DC Percentage and DC Value. Figure 5 shows the various disorders listed in Figs 3 and 4 with the AC/DC percentage on the abscissa and the DC value on the ordinate. The data in Fig 5 indicate a moderate correlation between the AC/DC percentage and the DC value ($r = .44$). However, if the data for unilateral vocal cord palsy are excluded, the correlation falls to the statistically insignificant value of $-.26$. An examination of Figs 3 and 4 shows that meaningful differences in AC/DC percentages are not accompanied by similar differences in DC values; Fig 5, in which the AC/DC percentages and the DC values are plotted together, demonstrates the lack of correlation between the two when the data for unilateral vocal cord palsy are excluded. These findings support the hypothesis that AC/DC percentage is expressive of the vocal cord's capacity for vibration.

This belief is further supported by the finding that

the AC/DC percentages in T2 and T3 cancers are smaller than in T1 cancers, and the percentage in the latter is smaller than that obtained for normals ($T3 = T2 < T1 < \text{normals}$; see Fig 5), while the DC values of the three types of cancer were not different. The results for acute and chronic laryngitis are also supportive: the AC/DC percentage for acute laryngitis is small, close to that for T2 and T3 cancer, while the percentage for chronic laryngitis is similar to that for normals — a finding in accord with our prediction, since the vocal cords in acute laryngitis are particularly stiff in comparison with chronic laryngitis.³

In summary, our results indicate that the AC/DC percentage is capable of differentiating the vibratory capacity of the various vocal cord disorders studied much more accurately than the DC value alone.

As shown by the standard deviation figures in Fig 3, a high degree of variability was found in the AC/DC percentages of all pathologic conditions examined. This variability, previously reported by Noguchi et al⁴ and Wilson and Starr,⁵ was not unexpected, since patients with the same diagnosis nevertheless suffer from various degrees of the disease. It would be difficult, therefore, to diagnose laryngeal disorders on the basis of the AC/DC percentage alone. One case in point is the identical percentages obtained for acute laryngitis and T2 cancer. We believe that the true value of the AC/DC percentage is an indication of the vibrational capacity of the cords, regardless of their specific pathologic changes. Since laryngeal disease is generally rather easy to diagnose with conventional methods, the clinical usefulness of the AC/DC percentage may lie in its efficacy in evaluating various therapeutic approaches.

Since the AC/DC percentage varies depending on the intensity of phonation,^{4,6} care should be taken to test the patient at a moderate level of intensity, neither too loud nor too weak. This can be achieved rather easily if the values of the same subject are compared serially during the course of treatment.

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CORNEAL AUTOIMMUNITY IN COGAN'S SYNDROME?

REPORT OF TWO CASES

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Autoimmune reactivity against corneal antigens is described in two patients with Cogan's syndrome, a nonsyphilitic deep interstitial keratitis with vestibuloauditory symptoms. In both cases corneal antibodies were found at the beginning or during an exacerbation of the disease. After administration of high doses of corticosteroids the corneal antibodies diminished. Interstitial keratitis can generally be controlled by local or systemic corticosteroids. The effect of corticosteroid therapy on the audiovestibular symptoms is variable. The possibility of an autoimmune pathogenesis of Cogan's syndrome is discussed.

KEY WORDS — autoimmune disease, Cogan's syndrome, corneal autoimmunity.

INTRODUCTION

In 1945 the ophthalmologist David Cogan was the first to describe a syndrome of nonsyphilitic deep interstitial keratitis with vestibuloauditory symptoms.¹ This disorder is currently known as Cogan's syndrome. More recent reports on this syndrome have indicated involvement of other organ systems and systemic vasculitis.^{2,3}

Although the cause of Cogan's syndrome is still obscure, an immunologic origin has been suggested by several authors. Hughes et al⁴ frequently found an elevation of the sedimentation rate in the acute stage of the disease. Edström and Vahlne⁵ described a patient in an acute stage of the syndrome in whom an episode of transient immunologic anergy was accompanied by an increased number of circulating T and B lymphocytes and signs of complement consumption. These observations were not confirmed in cases reported later.^{4,6,7} Hughes et al⁴ also demonstrated that an inner ear membrane extract could induce lymphocyte migration inhibition in a patient with Cogan's syndrome. Lymphocyte stimulation by eye-specific proteins (S antigen, outer rod segment, or scleroprotein) was described by Peeters et al.⁸ Arnold and Gebbers⁹ found antibodies directed against inner ear tissue and corneal epithelium in serum of patients with Cogan's syndrome. There is scattered evidence for human leukocyte antigen allotype associations in Cogan's syndrome, but the number of patients stud-

ied is still too small to draw significant conclusions from the data.^{4,10}

In Wegener's granulomatosis, polyarteritis nodosa, and rheumatoid arthritis with corneal involvement, a high incidence of circulating antibodies to corneal epithelium has been observed, which suggests an autoimmune cause.¹¹ In this paper two patients with Cogan's syndrome associated with systemic manifestations are presented. During the course of the disease, tests were repeatedly performed to detect the presence of circulating antibodies against the cornea. The results support the possibility that autoimmune reactions contribute to the development of Cogan's syndrome.

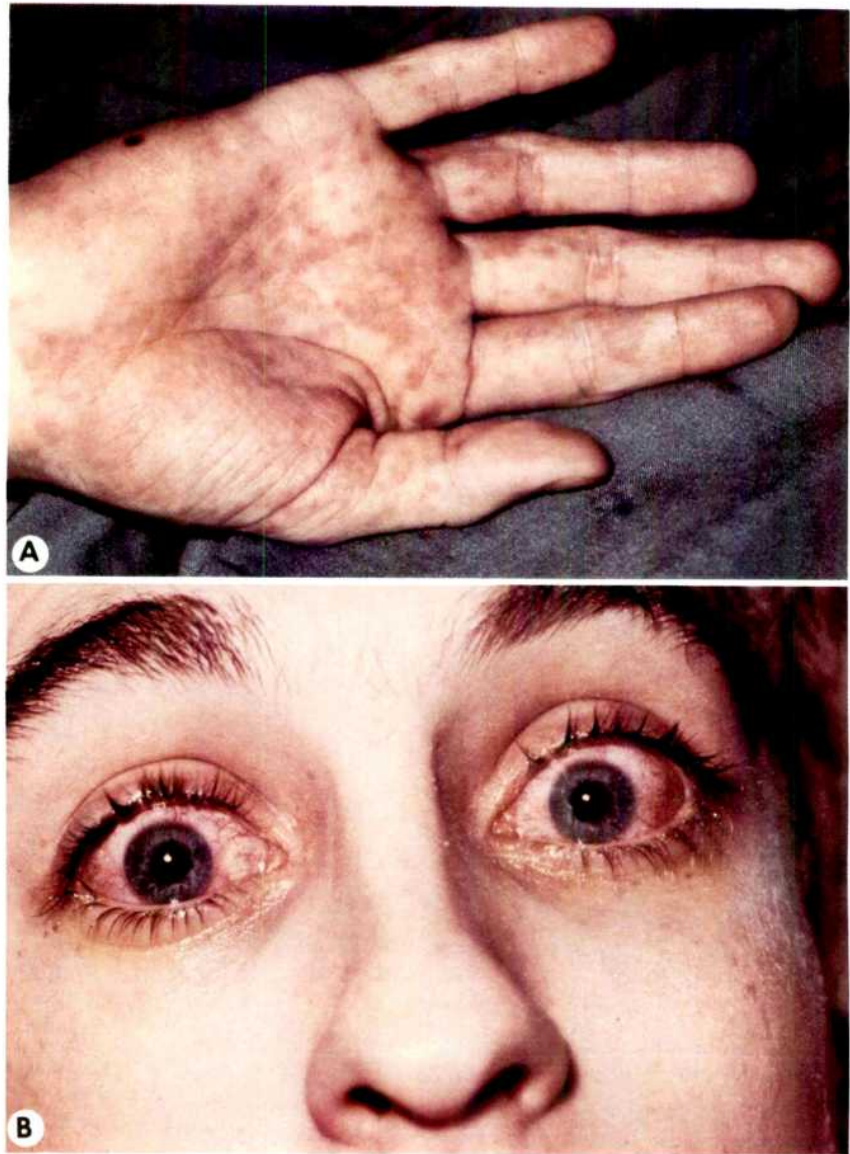
CASE REPORTS

Case 1. A 21-year-old man developed a mandibular abscess after extraction of a molar. Two days after drainage of the abscess he became very ill with severe headaches, poorly localized discomfort in the neck, lower back pain, and arthralgia, followed by abdominal discomfort 1 week later. He was admitted to the Department of Otorhinolaryngology, University Hospital Utrecht, 4 weeks after his first complaints. Besides the above-described symptoms, he had lost 12 kg in weight and suffered from intermittent fever, anorexia, fatigue, epistaxis, nausea and vomiting, and testicular pain. The patient complained of bilateral hearing loss with tinnitus and fullness in the ears.

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Fig 1. (Case 1) A) Erythema of palm of hand. B) Injected perilimbal vessels and conjunctivitis of both eyes.



An equilibrium loss without vertigo was noticed when he changed position. He furthermore suffered from pain in his eyes, photophobia, and conjunctival redness without diplopia.

On physical examination, thrombophlebitis of both legs and erythema of the palms of the hands and the soles of the feet were found (Fig 1A). A loud systolic murmur was heard on abdominal auscultation. There were no neurologic aberrations. Routine otorhinolaryngologic examination revealed no abnormalities and a normal tympanic membrane on both sides. Audiometry showed a slightly sloping sensorineural hearing loss of 30 dB for the right ear and 40 dB for the left ear. Similar losses were measured on speech audiometry, while speech discrimination was found to be normal (Fig 2A). There was no recruitment, tone decay was normal, and Békésy audiometry was of the cochlear type. The glycerol test was negative and

tympanometry was normal. Electronystagmography did not show spontaneous or positional nystagmus. On caloric examination, both labyrinths responded normally and symmetrically. A rotating chair nystagmogram revealed hypofunction. On ophthalmologic examination, interstitial keratitis with injected perilimbal vessels and conjunctivitis was observed (Fig 1B).

Routine laboratory findings showed normal values of blood chemistry and hematology except for an erythrocyte sedimentation rate of 74 mm/h. C-reactive protein value was 14.6. There was increased liver function and normal renal function. Thyroid function was normal except for a high thyroglobulin of 1,000 $\mu\text{g/L}$ (normal value is $<10 \mu\text{g/L}$). The cerebrospinal fluid showed an increased total protein level (0.72 g/L) and an elevated white blood cell count ($29/\text{mm}^3$) with 83% lymphocytes. No paraprotein was demon-

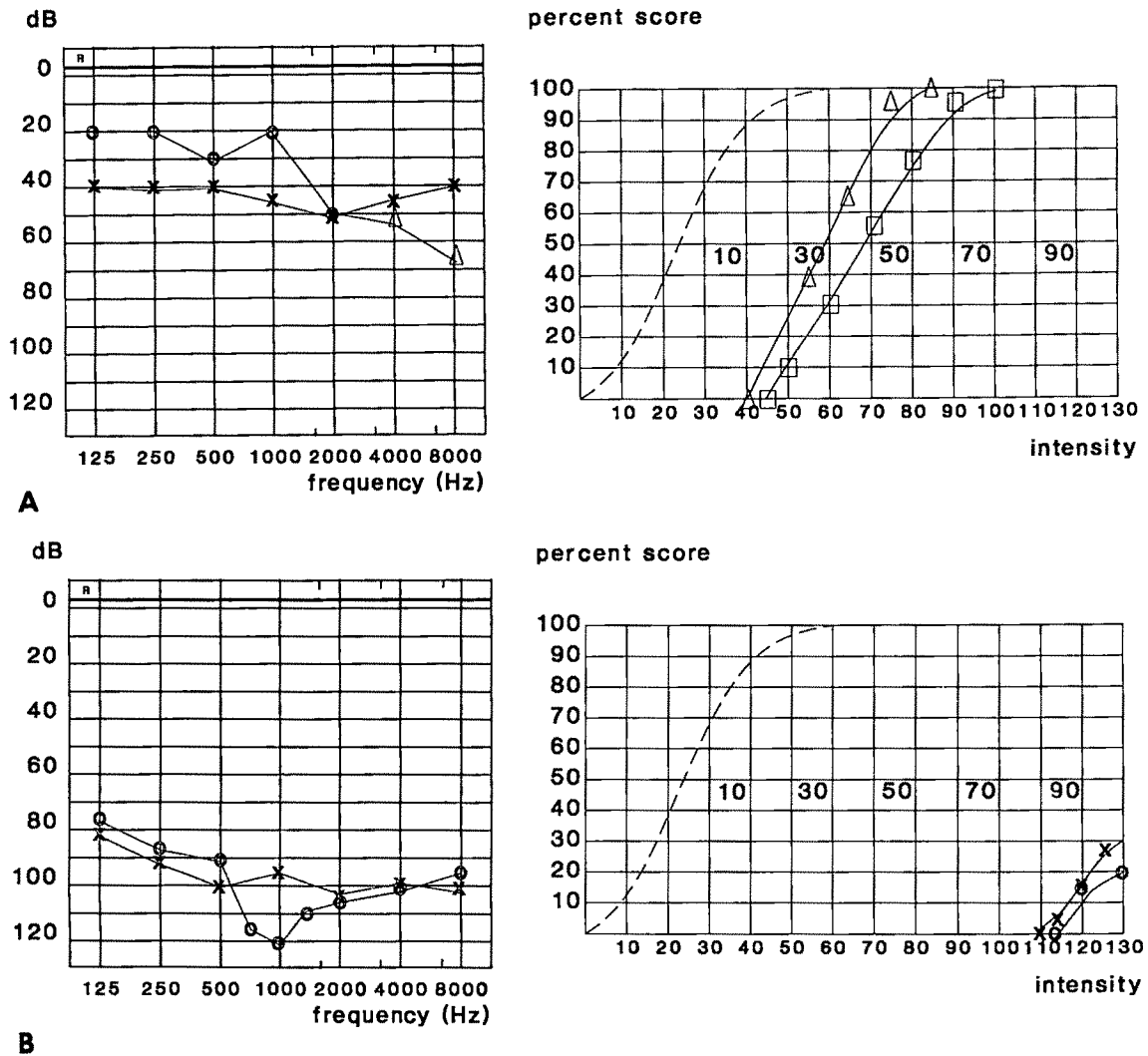


Fig 2. Pure tone and speech audiometry. A) Case 1. Air conduction, right ear, shown by O. Air conduction, left ear, shown by X. Second graph, discrimination scores. Right ear with masking shown by Δ. Left ear with masking shown by □. B) Case 2.

strable, and albumin and fibrinogen levels were normal. Immunoglobulin A was slightly elevated. Complement factors were normal, with a slight elevation of C3 and C1q. Antineutrophil cytoplasmic antibodies, circulating immune complexes, and antinuclear antibodies were normal. On radiographic examination, no abnormalities were observed (sinuses, thorax, polytomography, and abdomen including angiography). Computed tomography scans of the temporal bones, the cerebrum, the abdomen, and the thorax revealed no abnormalities. Radionuclear investigation and leukocyte and technetium scans showed no abscess or osteomyelitis. Bone marrow was normal and serologic tests for syphilis were negative. A complete screening of serum and cerebrospinal fluid for bacterial or viral causes of the disease revealed a herpes simplex virus titer elevation in serum from 16 to 64. Multiple cultures were negative. Biopsy of the skin, fascia, muscle, sural

nerve, jejunum, duodenum, pancreas, and liver did not show signs of vasculitis.

Initial treatment with broad-spectrum antibiotics was unsuccessful. After systemic administration of a high dosage of corticosteroids (60 mg prednisone daily), the patient's condition improved significantly. Before corticosteroid therapy, there was a slight improvement of hearing in both ears, which continued during corticosteroid therapy. The keratitis was cured with betamethasone eye drops. After 7 months, the hearing level in both ears had returned to normal.

Case 2. An 18-year-old man suffered from pain in his left eye with redness and photophobia, followed by vertigo, vegetative reactions, hearing loss, and tinnitus the next day. Two weeks later an exacerbation of his complaints occurred and he was admitted to a local hospital.

Otologic examination revealed a normal tympanic membrane on both sides. Audiometry showed a flat sensorineural hearing loss of about 90 dB for the right ear and a sloping sensorineural hearing loss of about 50 dB for the left ear. Ophthalmologic examination revealed an interstitial keratitis and uveitis of the left eye only. Visual acuity was normal in both eyes. There were no neurologic aberrations. Cerebrospinal fluid analysis and computed tomography of the cerebrum and petrous portion of the temporal bone revealed normal findings. The erythrocyte sedimentation rate was 6 mm/h, in the presence of leukocytosis without eosinophilia. The results of renal and liver function tests were normal. Immunologic tests were negative. On the basis of these clinical and laboratory findings, Cogan's syndrome was diagnosed.

The patient was first treated by high systemic doses of dexamethasone acetate and betamethasone eye drops. After 2 weeks the treatment was expanded to include plasmapheresis three times weekly. In spite of this treatment the clinical situation worsened, and he was referred to the Department of Otorhinolaryngology at University Hospital Utrecht.

The general patient history showed eczema of the arms and legs during childhood and complaints of asthma with allergy and hay fever. On admission there was a complete hearing loss and severe vertigo, whereas the symptoms in the left eye had diminished.

Physical examination showed a young man with a cushingoid appearance and asthmatic wheezing. Palpation of the abdomen was painful and there was myalgia of the legs without arthralgia. Routine otorhinolaryngologic examination revealed no abnormalities. Hearing loss was 100 dB in both ears, with severely impaired speech perception (Fig 2B). Electronystagmography showed no response to caloric stimuli or rotating chair nystagmogram testing on either side. There was no spontaneous or positional nystagmus. The interstitial keratitis of the left eye was almost cured.

Laboratory data showed a leukocytosis without eosinophilia. Erythrocyte sedimentation rate, liver and kidney function, and serum albumin and fibrinogen were normal. Paraproteins were not demonstrable. Immunoglobulin M was slightly elevated. Complement factors were normal, as were cryoglobulins. Autoantibodies, including rheumatoid factors and antineutrophil cytoplasmic antibodies, were not demonstrable. Some circulating immune complexes were present; the test for antiperinuclear factor was weakly positive. Serologic tests for syphilis were negative. Screening of serum for bacterial or viral infections was negative. A radiographic examination

revealed no abnormalities.

After admission to our hospital the patient was treated by cyclophosphamide and prednisone (during the first week, 50 mg and 25 mg, respectively, daily; during the second week, 100 mg and 25 mg; and during the third week, 150 mg and 25 mg). Meanwhile, betamethasone eye drops were given three times a day. Because of a slight improvement in hearing, a maintenance dosage of 15 mg prednisone daily was given. In the meantime a hearing device was prescribed.

Four months later, his clinical condition worsened again, with hearing loss on both sides and retroauricular pain. The patient complained of pain in the right eye (especially during eye movement), general illness, fatigue, headaches, arthralgia, and abdominal pain. An audiologic investigation revealed a loss of 120 dB on the right and 110 dB on the left. A routine ophthalmologic examination showed conjunctivitis of the right eye with injected perilimbal vessels but no interstitial keratitis. Scleral thickness of the right eye was demonstrated by computed tomography. An episcleritis was suggested. Except for an erythrocyte sedimentation rate of 50 mm/h and a leukocytosis, the routine laboratory data were normal. Immunologic research revealed slightly elevated C1q, immunoglobulins G and M, positive immune complexes (immunoglobulins G and M), and a slightly positive antiperinuclear factor.

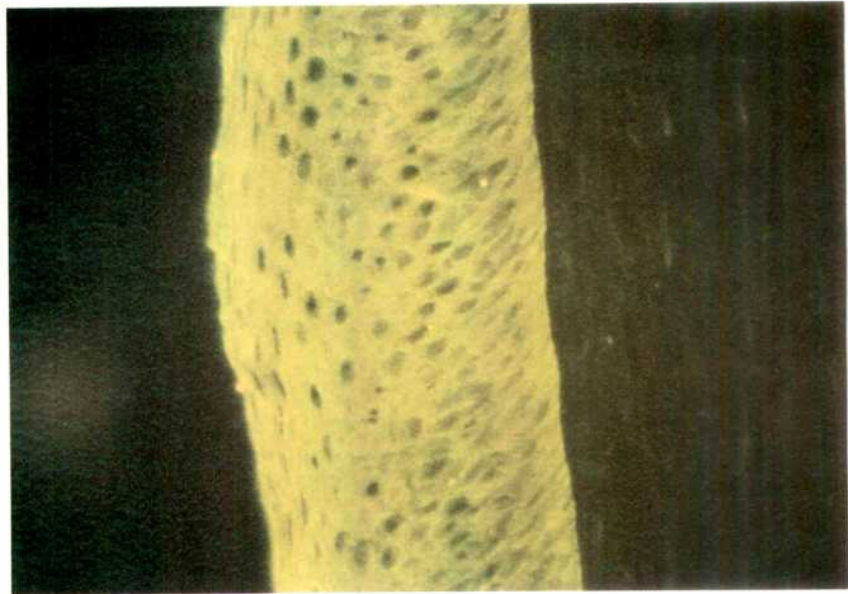
Because of this exacerbation, the patient was treated with a high dosage (1 g) of methylprednisolone for 3 days and atropine sulfate and dexamethasone-neomycin-polymyxin eye drops. In spite of the treatment, no improvement in the hearing occurred. Further therapy was therefore abandoned. After 3 months his general condition stabilized, with disappearance of the eye complaints.

Subtotal deafness, a slight tinnitus, and postural instability persist. The patient is supporting his lip-reading by means of a body hearing aid.

ANTIBODIES AGAINST CORNEAL ANTIGENS

Apart from the general immunologic investigations, we determined the presence of circulating corneal antibodies in the serum of both patients. Sera were obtained at the time of admission of the patients to our hospital, as well as before and after each treatment given. At the same time, samples were taken from healthy clinic staff to serve as controls (one woman and one man, mean age 24 years). Both control subjects were questioned concerning their previous medical history; there had been no otologic

Fig 3. (Case 1) Strongly positive immunofluorescence on bovine cornea.



or ophthalmologic complaints, and there was no history of contact lenses or of working or living in air-conditioned places. Circulating antibodies to corneal epithelium were assayed by an indirect immunofluorescence technique on bovine cornea. The sections were scored blindly by two investigators using the following classification: strongly positive (Fig 3), positive, and negative. Two types of immunofluorescence in the corneal epithelium were observed: 1) staining of cell membranes only, and 2) cytoplasm plus cell membrane staining. In addition, staining of the keratocytes was seen in the stroma. The methods used have been described by van der Gaag et al¹² and Kruit et al.¹¹

In case 1, before corticosteroid therapy was given, the immunofluorescence was strongly positive for the cytoplasm and slightly positive for the cell membranes of the corneal epithelium, and there was staining of keratocytes in the stroma. Five days after systemic corticosteroid administration the immunofluorescence still showed positive staining of the cytoplasm in the epithelium and keratocytes in the stroma, but the staining of the cell membrane had become negative.

In case 2, the patient had already been treated by corticosteroids and plasmapheresis in a local hospital before immunologic investigations could be carried out. During the first weeks after admission, the results of an immunofluorescence test on bovine cornea were negative. When his clinical condition worsened, a strong immunofluorescence in the epithelial layer of the cornea was found, but no staining of keratocytes. The staining of the cornea remained positive after treatment with a high dosage of methyl-

prednisolone. No circulating corneal epithelium antibodies were found in either of the controls.

DISCUSSION

In both patients, the characteristic symptoms of Cogan's syndrome were associated with systemic disease such as abdominal discomfort, anorexia, vegetative reactions, arthralgia, testicular pain, and headaches, as frequently found in autoimmune disease. Our investigation of immunity against corneal antigen, assayed by indirect immunofluorescence, may support an immunologic cause for this disease. In case 1, antibodies to corneal epithelium and keratocytes in the stroma were found before treatment with corticosteroids. Five days after corticosteroid treatment was started, the cytoplasm and stroma cells were still positive, whereas the cell membranes were negative. In case 2, no antibodies to corneal antigens were found when the patient was admitted to our hospital after his initial treatment elsewhere with dexamethasone and plasmapheresis. After an exacerbation of the disease, a strong serum reactivity to the epithelial layer of the cornea was observed. After therapy with high-dosage methylprednisolone the reactivity decreased. There seem to be correlations among the therapy given, the clinical condition of the patients, and the presence of antibodies to the cornea. Immunity to corneal antigens has been described previously in patients with Cogan's syndrome.^{8,9,13} The findings were not correlated with the therapy given; however, Hughes et al⁴ reported positive results of tests for lymphocyte migration inhibition and transformation during the acute stage of the disease. These results did not show any correlation with corticosteroid

therapy.⁴ In agreement with other investigators, we found nonspecific immunologic and hematologic phenomena in the acute phase of the disease, such as a slight elevation of immunoglobulins M and G and C1q; the presence of immune complexes and antiperinuclear factor; an elevated erythrocyte sedimentation rate; and leukocytosis with neutrophilia.⁴⁻⁹

In typical Cogan's syndrome, there is always interstitial keratitis.^{6,7,14} In our patients, however, the immunofluorescence of the epithelium was stronger than that of the stroma. This finding cannot be explained by our present knowledge. It might be the result of the fact that the corneal epithelium is the richest reservoir of antigens,¹⁵ whereas the relatively acellular stroma provides a more limited source of antigens.

In both patients, there was an amelioration of the ophthalmologic symptoms after topically and systemically administered corticosteroid therapy that is in agreement with the literature.^{6,7} The first patient had a slight improvement of hearing in both ears

before administration of corticosteroids, and the improvement continued during therapy. Seven months later, the hearing level in both ears had returned to normal. The second patient did not show any improvement in response to the various medications given. It is not known whether the hearing loss is self-limiting, as suggested by our first case. Most Cogan's syndrome patients are treated with high-dosage corticosteroids at an early stage of the disease. Vollertsen et al⁶ and Hughes et al⁴ found an amelioration of hearing in approximately 40% of the patients who were treated with systemically administered corticosteroids.

Patient 1 developed an abscess in the mandible 2 days before the initial symptoms appeared. We also found an elevated titer of herpes simplex in this case. Patient 2 suffered from eczema, asthma, and allergic rhinitis. It is possible that the anticorneal antibodies are secondary to tissue damage induced by an unknown cause. Although consistent evidence of infection is not found in the literature, a viral or bacterial cause of Cogan's syndrome is often postulated.^{5,6,16,17}

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GIANT AIR CELL OF THE PETROUS APEX: A POSSIBLE CAUSE OF FACIAL HYPALGESIA

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A giant air cell of the left petrous apex was found in a 23-year-old man with ipsilateral facial hypalgesia. The size of the giant air cell depicted on computed tomography was 1.5 x 2.0 x 2.0 cm. A coronal T1-weighted magnetic resonance image showed that the trigeminal nerve was compressed superomedially by a large signal void area that was probably a result of excessive pneumatization of the petrous apex. It is suggested that the facial hypalgesia was caused by the compression by the giant air cell of the petrous apex on the trigeminal nerve.

KEY WORDS — giant air cell, magnetic resonance imaging, petrous apex, trigeminal nerve.

INTRODUCTION

It is rare for pneumatization of the petrous apex to develop giant air cells. Doubis and Roub¹ were the first to report such a rare finding, in 1978. In Japan, Hosotani et al² reported a case in which the cause of autophony was giant air cells of the petrous apex. Our report describes a case of trigeminal hypalgesia for which a giant air cell of the petrous apex was most likely responsible.

CASE REPORT

A 23-year-old man, otherwise healthy, presented with the complaint of loss of sensation that he had noticed for the last 2 months on washing his face. Neurologic examinations revealed hypalgesia to pain in the left buccal and labial regions, which are innervated by the second branch of the left trigeminal nerve. The rest of the findings on otolaryngologic examination were negative, and no abnormal neurologic signs were detected. The laboratory investigations, including complete blood cell count, blood chemistry, and urinalysis, revealed no abnormalities. A radiograph of the skull indicated left and right asymmetry in the shape of the skull base (see Figure, A). Sinus x-ray films showed normal development and pneumatization of the maxillary, ethmoidal, and frontal sinuses. The ear films showed well-pneumatized mastoids. On tomographic views, an extremely large air cell was found in the left petrous apex,

overlapping the internal auditory canal (see Figure, B). Furthermore, axial computed tomography (CT) revealed that the giant air cell of the petrous apex extended near the sphenoid sinus with a size of 1.5 x 2.0 cm. No abnormalities were noted in the brain parenchyma.

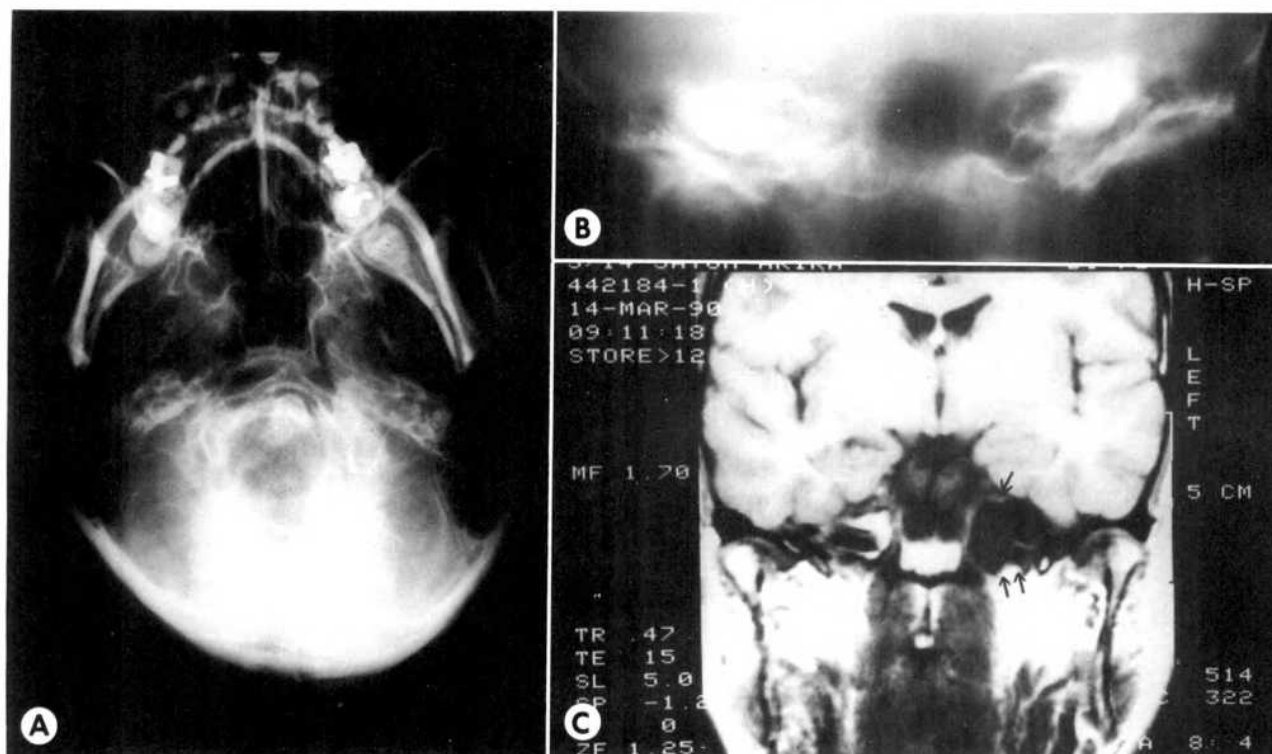
For further evaluation of the giant air cell, magnetic resonance imaging (MRI) was performed. A coronal T1-weighted image depicted the left trigeminal nerve in Meckel's cave of the left skull base to be compressed superomedially by a large signal void in the left petrous bone (see Figure, C). When compared with the CT findings, it was shown that this signal void area was a pneumatized cell of the petrous apex. The vertical diameter of the pneumatized cell was approximately 2.0 cm. The basilar artery was slightly inclined to the right with no obvious effects on the posterior cerebral and superior cerebellar arteries. Even in a 5-mm frontal section, Meckel's cave was asymmetric. Neuro-otologic investigations, including audiometry and auditory brain stem response, yielded normal findings.

From the above findings we inferred that the giant air cell of the petrous apex may alter the anatomic location of the trigeminal nerve around it and may eventually cause neurologic symptoms.

Over a period of 19 months after the initial visit, the extent and degree of hypalgesia of the left side of the

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Giant air cell of petrous apex. A) Axial skull x-ray. Asymmetric skull base is noted. B) Anteroposterior polytomogram shows large pneumatized cell in tip of petrous bone on left. C) Coronal T1-weighted magnetic resonance image indicates left trigeminal nerve (single arrow) is compressed superomedially by signal void area (double arrows) of basilar region.

face remained unchanged. The patient is being followed up as an outpatient, and progress of the hypalgesia related to the trigeminal nerve is under observation.

DISCUSSION

Giant air cells of the petrous apex were reported by Doubis and Roub¹ in 1978. According to their studies on the temporal bone tomograms of 1,600 patients, giant air cells, defined as cells with a diameter exceeding 1.5 cm, were observed in 15 patients (0.94%).

Excessive expansion of the bony air space is known by various names, including pneumocele, pneumatocoele, pneumosinus, pneumosinus dilatans, and others. However, as the term "-cele" may confuse this condition with other diseases, Benjamins³ suggested the term pneumosinus dilatans as the most suitable. Despite the abnormally expanded sinus, Jezegabel⁴ defined pneumosinus dilatans as a sinus filled with air alone, and lined by normal intact mucous membrane, that occurs frequently between puberty and adolescence. This condition is usually observed in the paranasal sinuses, and a few reports have illustrated an expanded frontal sinus. In Japan, Kitamura and Ishiura⁵ first reported on the giant air cells of the frontal sinus as pneumosinus dilatans. Giant air cells of the petrous apex are considered to be similar to pneumosinus dilatans derived from the temporal bone.

As etiologic factors, the following have been suggested^{3,6,7}: 1) congenitally abnormal elements, 2) trauma, 3) infection with aerogens during cavity closure, 4) positive pressure induced by a valviform action caused by a polyp, etc, 5) outflow of the contents due to mucocoele-induced internal pressure build-up, and 6) extreme pneumatization, due to abnormalities in the sinus wall. These factors are distinctly related to the paranasal sinuses, especially to the frontal sinus, and cannot be attributed to the temporal bone directly. In the present case, since there was no previous history of trauma or otitis media, congenital factors or an extreme pneumatization process were considered as possible causes.

There are only two reports on symptoms related to the giant air cells of the petrous apex. According to Kraus and McCabe,⁸ recurrent meningitis with cerebrospinal fluid leakage can be induced by a giant air cell, and they advocated a new entity: giant apical air cell syndrome. Hosotani et al² described a case of autophony and concluded that it could be induced by an increase of tympanic membrane compliance caused by a giant air cell. In the present case, the patient was thought to have hypalgesia due to compression of the trigeminal nerve between the pons and the trigeminal ganglion in Meckel's cave, induced by the giant air cell of the petrous bone.

In general, neurinoma, meningioma, epidermoid

cyst, aneurysm, and arachnoiditis are lesions of Meckel's cave that could produce trigeminal neuralgia. Moreover, neurovascular pressure is considered to be a factor in trigeminal neuralgia, as suggested by Jannetta.⁹ Of Fukushima's¹⁰ 1,533 cases, the compressing vessel was the superior cerebellar artery in 80%, the anterior inferior cerebellar artery in 6.4%, and the basilar artery in 6.6%. Although our patient was not affected by any paroxysmal pain of classic neuralgia and was not in the high-incidence age group, the possibility of involvement of the blood vessels around the trigeminal nerve cannot be excluded.

On CT, cranial nerves V, VII, and VIII cannot be visualized well without a contrast agent or air. However, MRI can depict cranial nerves without any contrast materials. It is excellent in illustrating any tumor of the cranial nerves and is said to be the first-choice examination when any abnormality in the cranial nerves is suspected.¹¹ The T1-weighted coro-

nal image, which best demonstrates the trigeminal nerve contrasted against the cerebrospinal fluid, generally provides the best technique for visualization of this cranial nerve. Daniels et al¹² emphasize the advantage of this technique because it can display a bilateral (left-right) comparison of the trigeminal nerve. Tash et al¹³ illustrated vascular compression on a T1-weighted image of a patient with trigeminal neuralgia caused by neurovascular compression that was confirmed by the surgical findings. In our case the normal distortion of the basilar artery was seen on MRI, but there is no evidence the basilar artery is compressed by the giant apical air cell, and no lesion was seen in the vessels themselves. These findings also reconfirm the benefit of using MRI.

If the symptoms are aggravated in the future, impairing the daily life of the present patient, the removal of petrous bone from the epidural space via a transpetrosal-transtentorial approach¹⁴ or a Lempert-Ramadier petrosectomy¹⁵ may be indicated.

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BOVINE TEMPORAL BONES AS A SOURCE OF INNER EAR ANTIGEN

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Modern immunologic techniques of immunostaining, immunoblotting, and creation of monoclonal antibodies are gaining wide application in studies of development, function, and pathology of the ear. These techniques require a source of inner ear tissue for production of antigen extract. Human tissue is not readily available, and other mammalian species common in auditory research are small in size. Bovine temporal bones are readily available, and the membranous portions of the inner ear are abundant and easily accessible. Herein we report our technique for acquisition and dissection of bovine temporal bones and preparation and preservation of inner ear antigen.

KEY WORDS — bovine animal model, immunology, inner ear, temporal bone.

INTRODUCTION

Modern immunologic techniques of immunostaining, immunoblotting, and creation of monoclonal antibodies are gaining wide application in basic research into the development and function of the ear, as well as in specific studies of pathologic processes such as genetic hearing loss and idiopathic progressive bilateral sensorineural ("autoimmune") hearing loss. These techniques all require inner ear tissue as a source of antigen extract for immunoreagents. While human inner ear tissue would be ideal for many such applications, it is difficult to obtain and offers only a small quantity of tissue. Typical laboratory mammals such as rabbit, rat, cat, or guinea pig are readily available, but also offer only small amounts of tissue from each specimen. In order to obtain a readily available and abundant source of membranous inner ear, we have begun using bovine temporal bones. Others have reported the use of bovine inner ear tissues in research.¹⁻³ However, these reports have given only limited description of the techniques for harvesting the membranes. This is a report of our technique for acquisition and dissection of bovine temporal bones and preparation and preservation of bovine inner ear antigen.

MATERIAL AND METHODS

Acquisition of Bovine Temporal Bones. Quartered calf skulls with the brain removed were obtained from a local abattoir and meat packing plant. Fresh quartered skulls are taken immediately upon availability and packed in crushed ice for transport to the research laboratory. The temporal bones are microdissected to remove the membranous components of the inner ear, which are then placed in phosphate-buffered saline (PBS), pH 7.4, and frozen at -40°C until

needed for antigen preparation.

Temporal Bone Microdissection. The posteroinferior quadrant of the bovine skull from foramen magnum to squamous temporal bone and from occiput to root of zygoma is massive, weighing several pounds. After an initial attempt using an adult cow, use of calf heads was deemed easier because of the smaller size and weight of the overall specimen without apparent difference in size of the otic capsule. The bony external auditory canal is more than 6 cm in length, making a lateral approach to the inner ear difficult and impractical. A medial approach along the petrous ridge and internal auditory canal (IAC) gains access to the membranous components of the inner ear with only a few millimeters of drilling.

All dura is removed from the middle and posterior fossa surfaces of the temporal bone. On these surfaces the otic capsule is chalky white and stands out in sharp contrast to surrounding bone (Fig 1A). With the aid of an operating microscope and cutting burs, drilling begins around the IAC on three fourths of the circumference, sparing the inferior one fourth (Fig 1B). Progressing from medial to lateral along the superior portion of the IAC exposes the facial nerve and geniculate ganglion area (Fig 1C). Immediately deep (inferior) and anterior to the first genu of the facial nerve is the basal turn of the cochlea. This turn is blue-lined from its anterior extent deep to the first genu of the facial nerve, anteromedially toward the posterior fossa surface of the petrous apex (Fig 1D). It is usually possible to gain some narrow exposure to the second turn of the cochlea by continuing this dissection anterolaterally from the basal turn toward the apex. Posterior to the IAC the vestibule, posterior semicircular canal, and crus commune are blue-lined

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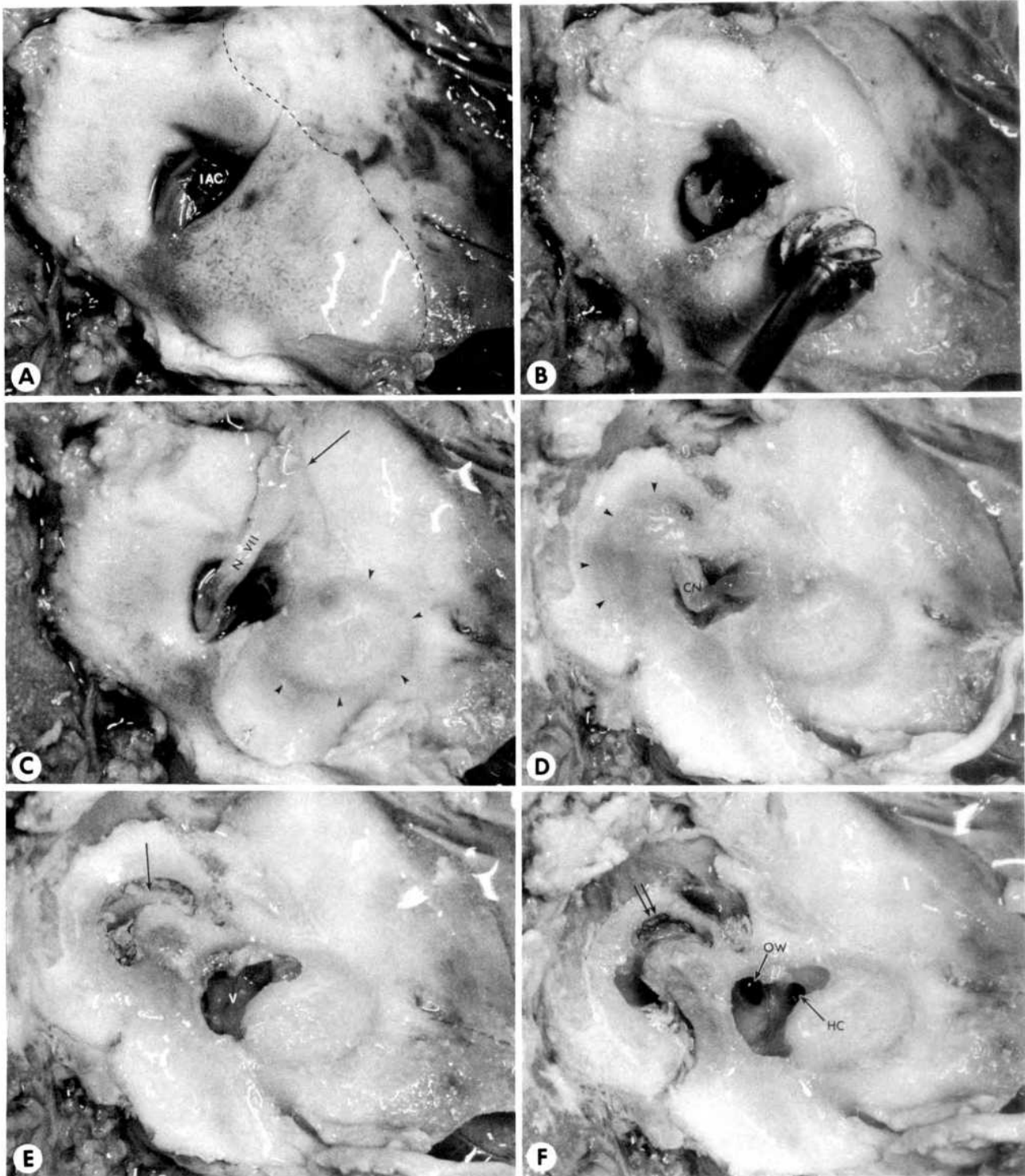


Fig 1. Temporal bone microdissection. A) Posterior fossa view of right temporal bone with dura removed. Note sharp demarcation of temporal bone from surrounding skull base. Dotted line — attachment site of tentorium cerebelli dividing middle fossa surface of temporal bone from posterior fossa surface, IAC — internal auditory canal. B) Cutting bur is used to drill away bone surrounding IAC from posterior to anterior. C) Facial nerve (N VII) to first genu and geniculate ganglion (arrow) is exposed and posterior semicircular canal (arrowheads) is blue-lined. D) Facial nerve has been removed and basal turn of cochlea (arrowheads) blue-lined. CN — cochlear nerve. E) Basal turn of cochlea has been opened, exposing osseous spiral lamina (arrow). Vestibule (V) is opened to allow removal of otolith organs and semicircular canal ampullae. F) Modiolus has been extracted to expose contents of second turn of cochlea (double arrows). Vestibule is widely opened to permit extraction of membranous contents of hook portion of cochlea and vestibular end organs. OW — oval window, HC — ampullated end of horizontal semicircular canal.

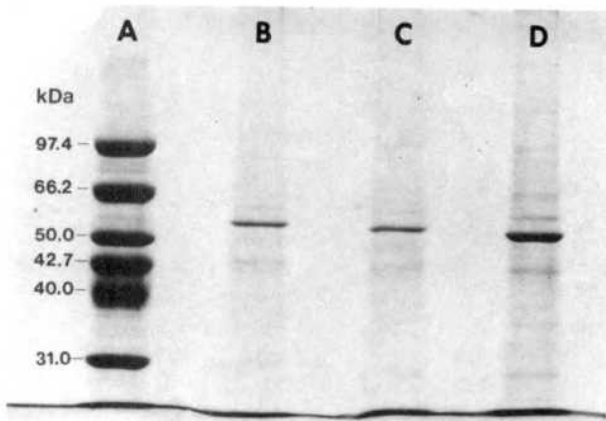


Fig 2. One-dimensional 12% sodium dodecyl sulfate gradient gel electrophoresis. Each lane dosed with 20- μ L sample composed of 10 μ L of specimen and 10 μ L of sample buffer, run at 40 mA for approximately 2 hours, and stained with Coomassie blue. A) Molecular weight standards. B,C) 7.1 mg/mL bovine inner ear (combined cochlear and vestibular) antigen extract. D) 6.0 mg/mL human cochlear antigen extract. Note high degree of banding homology between bovine and human samples.

as well. Throughout the drilling frequent irrigation or use of continuous suction irrigation is used to prevent overheating of the tissues. Once the cochlear and vestibular divisions of the inner ear are blue-lined, they are opened widely but superficially with diamond burs to expose the membranous structures of the inner ear (Fig 1E). These are extracted easily by using a combination of whirlybird elevators and cup forceps. The saccule and utricle are lifted from the vestibule, and then each of the three ampullae of the semicircular canals are removed. The membranes of the cochlea are removed from base to apex on the exposed superomedial surface of the cochlear spiral, and then the modiolus is cracked out with a stapes curette to gain access to the inferolateral portion of each turn. The membranes of the hook portion of the cochlea are most easily removed through the vestibule (Fig 1F). All tissue is placed directly into 0.5 mL chilled PBS solution as it is removed in order to reduce postmortem autolysis.

Antigen Extract Preparation. In a cold room, tissue obtained from microdissection of the temporal bones is teased apart and homogenized in 0.5 mL of PBS (pH 7.4). The homogenate is then subjected to four sonication intervals (Branson Sonifier 450) of 2 minutes each at 4°C. The resultant suspension is centrifuged at 3,000g for 30 minutes in the cold room and

the supernatant decanted and filtered through a 0.2- μ m filter. Protein content of this final extract solution is determined on the basis of optical density measurement by using a modified Lowry method as described by Bloch et al.⁴ Aliquots are diluted 1:10 in PBS and optical density is measured at 215 and 225 nm. Protein concentration is calculated by using the following formula: $[144 \times (OD_{215} - OD_{225})] \times \text{dilution factor} = \mu\text{g/mL protein concentration}$. The extract solution is then divided into aliquots and stored at -70°C.

DISCUSSION

Using the techniques described, we have been able to achieve extract concentrations in excess of 7.0 mg/mL from dissection of six temporal bones. Electrophoretic comparison of bovine inner ear antigen extract to human extract reveals a high degree of banding homology (Fig 2). Separation of the constituents of the extract by gel electrophoresis followed by Western blot assay for inner ear antibodies is being used as part of an ongoing project studying idiopathic progressive bilateral sensorineural hearing loss. Purification by gel electrophoresis could also be used as the initial step in production of monoclonal antibodies.

Use of cadaveric human inner ear tissue as a source of antigen had the complicating issues of postmortem autolytic changes and small quantity of tissue. This latter problem required repeat standardization of antigen content for each new sample, necessitating gradual depletion of our most potent antibody-containing serum samples. The virtually unlimited supply of bovine inner ear tissue and the ease of dissection (less than half an hour per pair of temporal bones) make it feasible to pool tissue from many animals in order to have a large quantity of antigen that may be standardized once, stored at -70°C, and used repeatedly when needed. Standardization of antigenicity is a chronic problem in immunostaining and immunoblotting techniques. Even commercial immunoreagents require standardization at the time of use to ensure reliable interpretation of results. Large pools of antigen reduce interspecimen error by applying the same antigen solution to each sample. In a longitudinal, prospective study such as our work on idiopathic progressive bilateral sensorineural hearing loss, the accuracy of data is greatly improved by having a long-term, stable supply of antigen to use throughout the duration of the study.

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QUANTITATIVE ULTRASTRUCTURAL STUDY OF CAT ABDUCENS INTERNEURONS

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Abducens interneurons project to the medial rectus subdivision of the contralateral oculomotor nucleus and have a role in the mediation of horizontal conjugate gaze. Two types of interneurons have been reported based on shape (fusiform and circular) and differences in organelles. In this study, 41 abducens interneurons from three young adult cats were examined in the transmission electron microscope and were classified, on the basis of eccentricity (e), as circular ($e < 0.82$; $N = 18$) or fusiform ($e \geq 0.82$; $N = 23$). The volume fraction of nucleus, nucleolus, mitochondria, rough endoplasmic reticulum, polyribosomes, and Golgi complex and the number of synaptic profiles per 100 μm of membrane were determined. Although there is a qualitative difference in these cell types, statistical analyses indicate no significant differences in organelle content, mean area, number of synaptic profiles per 100 μm of membrane, or diameter. While the differences in shape may possibly indicate different functional groups, this notion is not supported by the variables examined or by physiological studies.

KEY WORDS — abducens nucleus, cat, interneurons, ultrastructure.

INTRODUCTION

The abducens nucleus is located immediately below the facial genu, extending from the rostral limit of the lateral vestibular nucleus to the rostral portion of the descending vestibular nucleus.¹ Intraaxonal labeling studies indicate that the nucleus consists of motoneurons that project to the lateral rectus muscle and interneurons that project via the medial longitudinal fasciculus to terminate in the contralateral medial rectus subdivision of the oculomotor nucleus.²⁻⁵ Using horseradish peroxidase (HRP) retrograde labeling techniques, Spencer and Sterling⁵ estimated that 25% of the nucleus consists of interneurons, while Steiger and Büttner-Ennever⁶ used the double labeling method to report that 50% of the nucleus consisted of interneurons.

Interneurons in the cat are spread throughout the rostral-caudal length of the nucleus, while in the rat,⁷ guinea pig,⁴ and chick⁸ the interneurons are almost exclusively in the rostral two thirds. These results show that the motoneurons and interneurons are intermingled to a greater extent in mammals with highly developed binocular, frontal vision and conjugate gaze than in lateral-eyed animals. Highstein and Baker⁹ and Carpenter and Batton¹⁰ concluded that in the cat the interneurons play a major role in horizontal conjugate gaze and that interruption of their projec-

tions results in ophthalmoplegia.

Two cytologically distinct types have been described at the light and electron microscopic level. At the electron microscopic level one type is characterized as a fusiform cell with an invaginated nuclear membrane and a poorly developed rough endoplasmic reticulum (RER), and the other as a multipolar or circular type resembling abducens motor neurons with a well-developed cisterna of RER.^{5,8,11}

This study was undertaken to provide quantitative information regarding the ultrastructure of the abducens interneuron in the cat. Point counting techniques were used to determine the volume fraction of mitochondria, RER, Golgi apparatus, polyribosomes, nucleus, and nucleolus. The mean number of synaptic profiles (SPs) per 100 μm of membrane was also determined. No statistically significant differences in cell types could be found in any of the variables analyzed.

MATERIALS AND METHODS

Three young adult cats (2.03 to 2.9 kg) obtained from the Institutional Laboratory Animal Resources were used in this study. The cats were anesthetized with 30 mg/kg intravenous Nembutal supplemented with intramuscular ketamine hydrochloride, and intubated orotracheally. A midline scalp incision was

From the Department of Otolaryngology and Communication Sciences, State University of New York Health Science Center at Syracuse (all authors), and Veterans Administration Medical Center (Gacek), Syracuse, New York. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the State University of New York Health Science Center at Syracuse.

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made over the occiput, and the underlying muscles were reflected laterally, exposing the bone over the cerebellar hemispheres. The bone overlying the vermis and part of the cerebellar hemispheres was removed, the dura incised, and the anterior vermis retracted from the inferior colliculi to expose the rostral portion of the fourth ventricle and the posterior aspect of the sylvian aqueduct. The midline sulcus separating the medial longitudinal fasciculus, in the caudal portion of the sylvian aqueduct, served as a landmark for the injection into the oculomotor nucleus. A glass micropipette (tip diameter 50 to 75 μm) was inserted to the right of midline and directed rostroventrally into the oculomotor nucleus. After 3 μL of 20% HRP (Sigma type VI) in saline was injected, the pipette was withdrawn and Gelfoam was used to seal the pipette tract. The operative site was loosely sutured closed with chromic suture and the skin was tightly closed.

Approximately 18 to 20 hours after HRP injection, the animals were painlessly killed under general anesthesia, and intracardiac perfusion was performed by clamping the descending aorta, opening the right atrium, and cannulating the ascending aorta through the left ventricle. Ringer's solution (250 mL at 37°C), driven by gravity, was followed by 500 mL of 0.12 mol/L phosphate buffer containing 1% paraformaldehyde, 3.5% glutaraldehyde, and 34 mg/L of calcium chloride at 37°C, pH 7.2 to 7.4. An additional 1 L of the same fixative at 4°C was perfused by means of a peristaltic pump. Total perfusion time with the double aldehyde fixative was limited to 1 hour.

Tissue Preparation. A 5 x 5-mm block of tissue containing the left abducens nucleus was removed from the brain stem, left in 3.5% glutaraldehyde for 3 hours at room temperature, and rinsed several times with the same buffer, and vibratome sections were cut at 60 μm . The sections were serially collected and reacted for HRP according to the method of Malmgren and Olsson.¹² The labeled cells were then dissected from the sections in the shape of a trapezoid to maintain orientation (longest vertical leg placed laterally). Each trapezoid was photographed and the position of each labeled cell marked. The trapezoids were rinsed in buffer, placed into 1% osmium tetroxide for 1 hour, washed in sodium maleate buffer (pH 6.0), stained en bloc with uranyl acetate, dehydrated in a graded ethanol series, and embedded in Spurr's embedding medium.

A reference notch was made in one side of each block, the block was photographed, and the distance between the block face and the notch was measured. Semithin serial sections were cut with a glass knife, the block was photographed again, and the distance

between the block face and the reference mark was remeasured. By dividing the difference of the first and second measurements by the number of sections, an average section thickness was calculated (2.5 to 4.7 μm). By placing these sections serially on a subbed slide, individual cells could be followed from section to section. In a random fashion—either every other section for cells that were present in less than 12 sections, or every third section for those that were present in more than 12 sections—the sections were remounted on blank plastic blocks. Ultrathin sections (60 to 90 nm) were cut with a diamond knife, mounted onto single-slotted 1 x 2-mm copper grids coated with formvar, stained with uranyl acetate and lead citrate,¹³ and examined in an electron microscope (JEOL 100-S).

The cells were identified at magnifications ranging from x500 to x1,000. Electron micrographs of three to five sections from each cell were taken at x6,000 and montages were assembled (final magnification approximately x18,000). With the aid of a Numonics 1224 x-y digitizer interfaced to a DEC PDP 11/73, the perimeter (in micrometers) and area (in square micrometers) were calculated by tracing the cell membrane, excluding any dendritic or axonal processes. After random placement of a point counting lattice, consisting of points spaced at 2-cm intervals, volume fractions were calculated for the nucleus, nucleolus, mitochondria, RER, polyribosomes, and Golgi complex. A minimum of five synaptic vesicles and synaptic membrane specialization were required to be present if an SP was to be included in the count. The total number of SPs per cell was then divided by the total perimeter (in micrometers). As a measure of cellular shape, the eccentricity was determined for each cell profile from the section containing the nucleus and nucleolus by using the formula

$$(1) \quad e = \frac{\sqrt{A^2 - B^2}}{A}$$

where A is the semimajor axis and B is the semiminor axis. Since the eccentricity for these cells represented a continuum from circular ($e = 0.2672$) to fusiform ($e = 0.9641$), it was difficult to decide where to divide the cells into the different shape categories. Seven independent observers were asked to classify each cell as circular or fusiform in an attempt to find a dividing point. Their responses were pooled and the cells classified as circular ($e < 0.82$) or fusiform ($e \geq 0.82$) on the basis of these judgments.

The diameter of each cell was calculated by using the formula

$$(2) \quad D = \sqrt{\frac{\pi}{4} \times Ar}$$

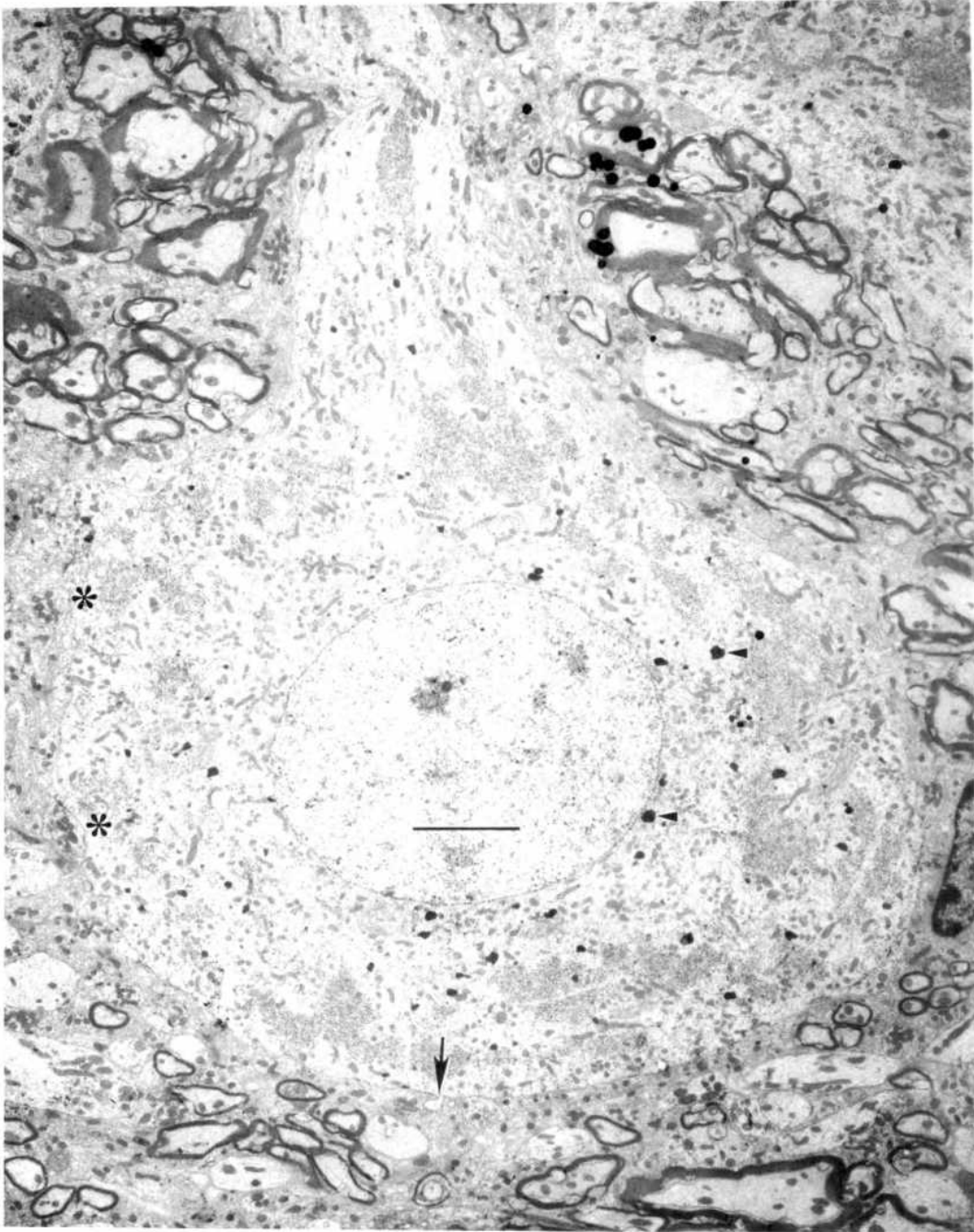


Fig 1. Electron micrograph of cell profile classified as circular on basis of eccentricity (0.754). Cell demonstrates intracellular horseradish peroxidase label (arrowheads), some synaptic profiles (asterisks), and somatic spine (arrow). Bar — 5 μ m.

where D is diameter and Ar is the mean area from the section data. It should be pointed out that this formula assumes a circle; results of this calculation (especially for the fusiform cells) may have little meaning as to the true shape of these cells; these data were only used for comparisons with results from other laboratories.

Data from each section were totaled and the mean for each variable was used in the analyses. All statis-

tical analyses were performed by using BMDP statistical software (BMDP Statistical Software, Los Angeles, Calif). A one-way analysis of variance¹⁴ was performed to determine group differences, and a probability value of <0.05 was set as the level of significance for rejecting the null hypothesis. In all analyses, the assumption of homogeneity of variance was tested and confirmed by using Levene's technique.¹⁵ Pearson's correlation coefficient¹⁴ was calculated for all variables. K-means cluster analysis

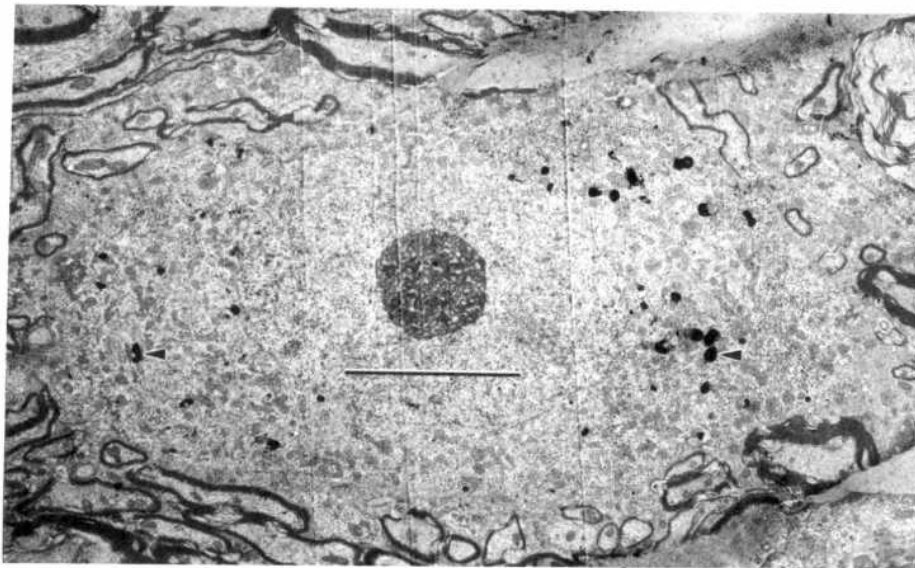


Fig 2. Electron micrograph of cell profile from fusiform group (eccentricity = 0.8879) showing intracellular horseradish peroxidase label (arrowheads). Bar — 5 μ m.

was also performed.¹⁶

RESULTS

Qualitative Observations. Although the shapes and sizes of the interneurons varied considerably, most intracellular organelles appeared to remain fairly constant in quantity and appearance. The RER cisternae were well organized in some of the circular cells and rather diffuse in others. This same heterogeneity of RER cisternae was also found in the fusiform cell group. Clefts in the nuclear membrane were no more prevalent in fusiform cells than in circular cells. A few somatic spines were seen in both types of cells. The typical appearances of circular and fusiform abducens interneurons are shown in Figs 1 and 2, respectively.

Quantitative Data. In general, the interneurons were small cells having an average area of $545 \mu\text{m}^2 \pm 224$ with a range of 274 to $1,269 \mu\text{m}^2$, and an average diameter of $25.78 \pm 5.24 \mu\text{m}$ with a range of 15.43 to $40.19 \mu\text{m}$. The number of SPs per 100 μm ranged from 0.0 to 8.49 with a mean of 2.03 ± 1.93 . There were a number of cells on which no SPs were found that met the criteria. However, there were SPs containing synaptic vesicles adjacent to the plasma-lemma, but they did not have any synaptic specializations. Given this, it is likely that there are synapses in other cellular regions and our sampling missed them, since it was somewhat limited. Even considering this possibility, it is likely that the number of synapses on these cells is very low.

The means and standard deviations for the volume fraction percent of the various organelles in the 41 cells were as follows: mitochondria 14.75 ± 2.38 , RER 20.69 ± 6.19 , Golgi 0.43 ± 0.38 , polyribosome 28.14 ± 9.07 , nucleus 13.85 ± 6.38 , and nucleolus

0.58 ± 0.40 .

When the cells were divided into circular and fusiform on the basis of their eccentricity there was an apparent difference in the amount and organization of the RER. However, quantitative data indicate that there was no significant difference in this or any of the other variables. The raw data for all of the variables from these two cell groups are presented in Tables 1 and 2. Distribution plots of the results from each cell type for volume fractions of mitochondria, RER, and area as well as SPs per 100 μm are shown in Fig 3. As can be seen, there is little difference between these groups. Pearson's correlation coefficient indicates no correlations among any of the variables. To determine if there was any regional distribution of the cell types, the cells were grouped according to the location in the abducens nucleus from which they were taken: caudal, intermediate, or rostral. Analysis failed to indicate any regional differences based on the variables measured. K-means cluster analysis using all of the variables in the data matrix also failed to separate these cells into any distinct groups.

DISCUSSION

The abducens nucleus of the cat is composed of at least two functionally different neurons: motoneurons that innervate the lateral rectus and retractor bulbi muscles,^{5,17,18} and interneurons that project to the contralateral medial rectus subnucleus and convey signals involved in the coordination of horizontal conjugate gaze.^{9,19} The coordination of the medial and lateral rectus muscles is provided by excitatory projections of the interneurons to the contralateral medial rectus motoneurons.^{20,21} These two types of abducens neurons have been shown to be scattered throughout the rostral-caudal length of the nucleus in

TABLE 1. DATA FOR CIRCULAR CELL GROUP

Area (μm^2)	Diameter (μm)	Volume Fraction Percentages						SPs per 100 μm	Eccen- tricity	
		Mito- chondria	Nucleus	Nucleo- lus	RER	Golgi	Polyribo- somes			
382	22.05	16.08	17.12	0.92	13.75	0.24	42.07	5.96	0.6328	
319	20.14	15.37	13.86	1.02	11.61	0.10	43.74	6.47	0.7954	
673	29.28	12.85	15.24	1.04	16.71	0.39	38.20	3.59	0.7555	
274	18.67	12.40	8.41	1.59	19.49	1.16	23.64	3.85	0.6178	
654	28.85	16.03	10.37	0.67	23.84	0.78	27.94	2.58	0.8162	
521	25.76	14.09	14.13	0.53	19.37	0.53	23.73	1.72	0.7092	
1,269	40.19	13.00	19.77	0.57	19.96	0.32	26.94	3.51	0.7454	
457	24.13	12.00	24.75	0.44	22.75	0.19	19.22	0.58	0.7775	
618	28.04	14.25	15.64	0.18	23.11	0.36	25.01	2.15	0.4482	
367	21.61	14.92	26.59	0.93	20.20	0.00	22.92	0.93	0.2672	
279	18.84	15.29	18.48	0.54	25.22	0.79	25.59	1.31	0.8171	
417	23.05	16.39	11.94	0.07	29.34	0.56	23.80	2.43	0.7740	
342	20.89	17.10	14.74	0.00	17.96	0.44	23.70	1.25	0.7332	
786	31.63	16.51	12.77	0.22	24.13	0.24	18.71	0.00	0.6092	
688	29.59	15.61	11.64	0.68	29.56	0.21	22.70	0.00	0.5894	
835	32.61	16.78	10.42	0.32	20.51	0.06	27.89	0.65	0.4638	
481	24.74	13.26	9.56	0.78	25.07	0.11	22.94	0.00	0.7421	
932	34.44	15.47	17.37	0.35	20.94	0.06	25.60	0.58	0.3025	
Mean	571	26.36	14.86	15.16	0.60	21.31	0.36	26.91	2.09	0.64
± 256	± 5.92	± 1.55	± 4.82	± 0.39	± 4.57	± 0.30	± 6.94	± 1.89	± 0.17	

RER — rough endoplasmic reticulum, SPs — synaptic profiles.

RER — rough endoplasmic reticulum, SPs — synaptic profiles.

mammals with binocular frontal vision, with the only grouping being a tendency for the small fusiform cells to be located adjacent to the facial genu.¹⁸ The

morphology of these neurons overlaps considerably, making their identification at the light microscopic level difficult. One morphologic difference between

TABLE 2. DATA FOR FUSIFORM CELL GROUP

Area (μm^2)	Diameter (μm)	Volume Fraction Percentages						SPs per 100 μm	Eccen- tricity	
		Mito- chondria	Nucleus	Nucleo- lus	RER	Golgi	Polyribo- somes			
614	27.96	15.76	14.10	0.64	12.62	0.18	40.77	3.40	0.9127	
187	15.43	17.10	9.72	0.50	14.40	0.17	30.49	2.58	0.9150	
278	18.82	14.35	8.30	1.31	15.69	0.00	52.38	5.05	0.8793	
424	23.23	16.60	7.94	1.20	10.65	0.00	51.98	3.88	0.8899	
312	19.92	15.61	8.68	1.37	10.97	0.51	50.13	2.74	0.9106	
340	20.82	14.93	7.28	0.61	12.14	0.52	36.99	1.90	0.8660	
384	22.10	8.50	8.47	0.65	15.47	1.15	27.91	3.18	0.9126	
470	24.45	14.45	7.57	0.71	16.04	0.85	30.77	8.49	0.9183	
301	19.59	9.91	27.20	0.84	9.07	1.44	22.77	3.03	0.8792	
918	34.19	15.79	4.79	0.00	27.83	0.12	22.04	1.48	0.8728	
646	28.67	14.24	17.86	0.08	24.26	0.70	22.57	2.51	0.9399	
448	23.88	9.34	30.43	0.85	19.28	0.98	20.42	0.00	0.9499	
430	23.41	8.87	24.94	0.32	19.06	1.09	22.74	1.39	0.9461	
368	21.56	13.73	7.90	0.00	25.59	1.15	23.47	0.76	0.8415	
472	24.52	18.43	17.91	0.88	20.51	0.11	26.05	2.11	0.8876	
818	32.28	16.33	11.70	0.64	36.11	0.31	16.04	0.00	0.9330	
720	30.28	17.33	10.23	0.00	25.71	0.18	22.13	0.49	0.8321	
866	33.20	17.02	10.08	0.30	27.17	0.36	19.56	1.14	0.9615	
575	27.06	16.09	20.18	0.59	22.80	0.62	22.83	0.45	0.9197	
607	27.80	16.00	15.50	0.47	18.31	0.32	34.64	0.39	0.9365	
565	26.83	18.00	13.24	0.28	19.95	0.13	25.17	0.00	0.8347	
698	28.81	16.28	10.00	0.00	30.34	0.19	24.33	0.00	0.9005	
603	27.72	12.64	11.16	0.54	30.96	0.18	23.13	0.80	0.9031	
Mean	524	25.33	14.67	12.83	0.56	20.21	0.49	29.11	1.99	0.90
± 192	± 4.86	± 2.86	± 7.22	± 0.40	± 7.17	± 0.42	± 10.33	± 1.96	± 0.04	

RER — rough endoplasmic reticulum, SPs — synaptic profiles.

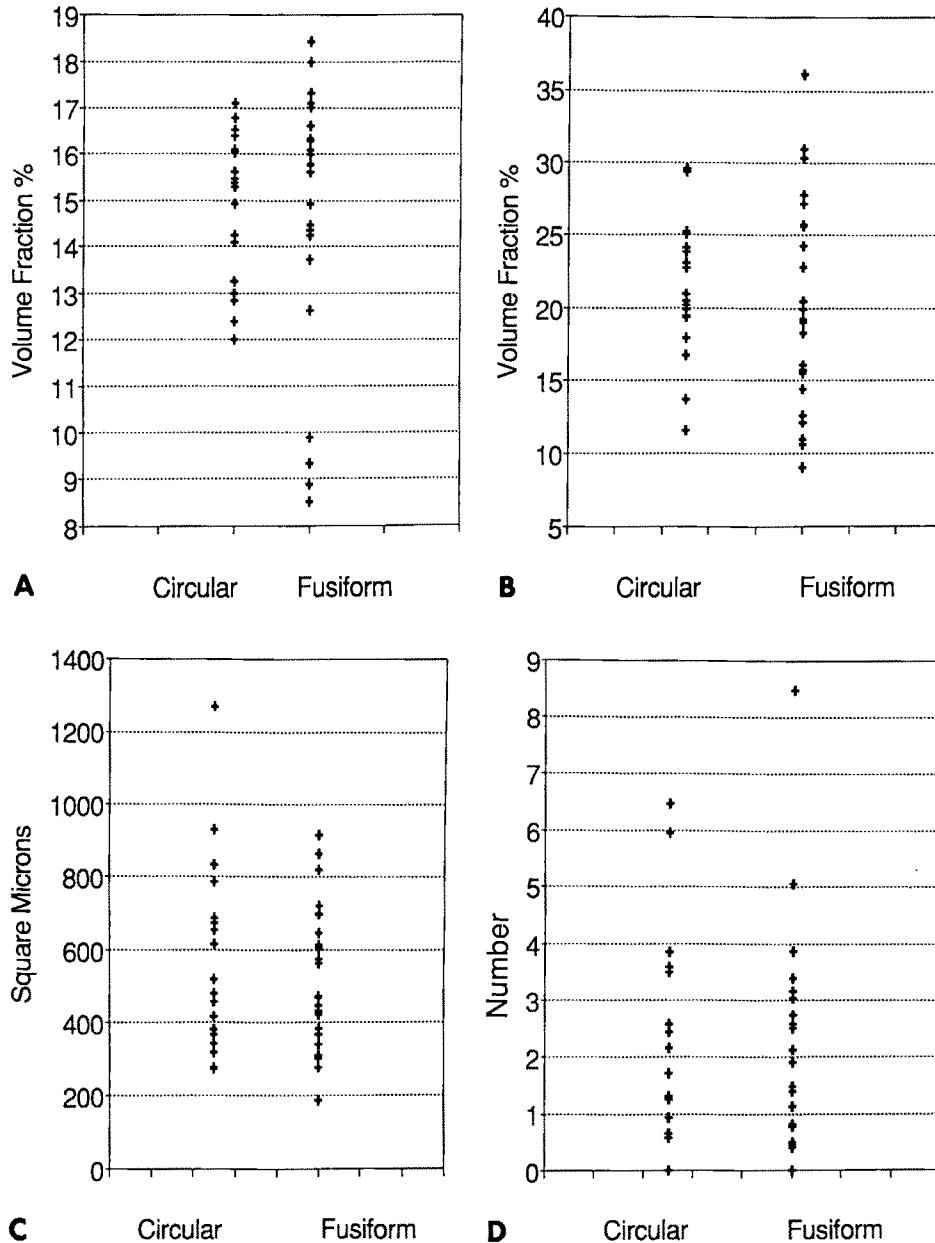


Fig 3. Distribution plots for circular and fusiform cell profiles. A) Volume fraction percent for mitochondria. B) Volume fraction percent for rough endoplasmic reticulum. C) Area. D) Number of synaptic profiles per 100 μm . Each shows no statistical difference between groups.

abducens interneurons and motoneurons is in their dendritic branching pattern¹⁸; the dendrites of interneurons tend to be thicker and less complex than those of motoneurons. Attempts to distinguish these cells by their ultrastructure have not been successful.^{5,11}

This study represents the first ultrastructural quantitative assessment of the intracellular organelles and somal SPs of the abducens interneurons. The presence of two different types of interneurons⁵ (fusiform cell body having a poorly developed RER and nuclear membrane invaginations; circular or multipolar having well-developed RER cisternae and a smooth, rounded nuclear membrane) was not confirmed in this study.

We found 10 times fewer SPs per 100 μm than reported by Spencer and Sterling⁵ (2.03 ± 1.93 compared to 21.4 ± 19.5 , respectively). One possible explanation for this difference is that Spencer and Sterling counted the SPs contacting the soma from a single section containing nucleus and nucleolus, while in our study, SPs were counted on three to five sections taken at random levels through each cell and averaged. However, this explanation is unlikely, because the difference was still apparent when the sections through the same cellular regions were examined in this study. A more plausible explanation is that the criteria of functional SPs used by Spencer and Sterling (not given in their report) were less restrictive than those employed in the present study. The criteria for an SP to be included in our counts were the

presence of at least five synaptic vesicles and synaptic membrane specialization. Many SPs seen in our study met only one of our criteria and were therefore excluded from the count.

The diameters of the abducens interneurons in this study were similar to those reported by Highstein et al,¹⁸ who used the average of the long and short axes for their diameter determinations. A valid comparison between our data and those of Spencer and Sterling⁵ could not be made, since a description of their method used for this determination was not given.

When the interneurons of our study were grouped by shape as fusiform or circular, no differences were found between the groups in the volume fraction of the organelles (RER, mitochondria, nucleus, nucleolus, Golgi complex, polyribosomes), area, diameter, or somal synaptic contacts. This result lends support to physiological studies^{18,22} reporting that there is little difference in firing rates or intraburst frequencies among the interneurons, regardless of size or shape. Differences have been reported in the trajectory of the interneuron axon collaterals. In the cat, some interneurons have axon collaterals within the contralateral medial longitudinal fasciculus that are directed toward either the prepositus hypoglossi nucleus or the reticular formation, and some have no

collaterals at all. Similar results have also been reported for the monkey,²² in which three classes of interneurons were described, one having no collaterals and the others having collaterals that terminate in the intermediate and/or caudal interstitial nucleus of the medial longitudinal fasciculus. While the study presented here demonstrates a homogeneous cell population, in agreement with current physiological data, the differences in axon collaterals may have functional significance. This may become apparent once additional morphological data on the dendritic processes are collected and physiological testing is completed.

CONCLUSIONS

Our quantitative analysis for volume fraction of mitochondria, RER, Golgi apparatus, polyribosomes, nucleus, and nucleolus as well as mean area, diameter, and SPs per 100 μm of cell membrane showed no statistically significant difference between circular and fusiform abducens interneurons. This result supports current physiological studies that have shown no difference in the activity of interneurons regardless of size or shape. However, it is possible that there are functional differences between cell types based on the termination of their axon collaterals. More extensive morphological data and physiological testing are needed to clarify these differences.

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The American Diopter and Decibel Society will hold its biennial meeting January 16-23, 1993, at the Westin Camino Real in Puerto Vallarta, Mexico. Abstracts are currently being accepted. For further information, contact Robin L. Wagner, American Diopter and Decibel Society, 3518 Fifth Avenue, Pittsburgh, PA 15213; fax (412) 647-8720, phone (412) 647-2227.

ANATOMY OF THE GUINEA PIG TEMPORAL BONE

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The middle ear of guinea pigs has long been used for experimental studies, but no detailed information about its temporal bone anatomy is available. In 18 adult guinea pigs, the temporal bone, eustachian tube, and inner ear anatomy, in addition to the anatomy of the middle ear, were investigated under the dissection microscope. In addition to properties of the eardrum, ossicles, air cell system, and cochlea previously described, the appearance of Huschke's foramen and the crista stapedis in an adult guinea pig ear, the structure of the eustachian tube, the architecture of the internal auditory canal, and the communication of the mastoid cells with the tympanic bulla are described. Differences and similarities among guinea pigs, other experimental animals, and humans are discussed to show the advantages and disadvantages of the guinea pig ear for experimentation.

KEY WORDS — anatomy, guinea pig, temporal bone.

INTRODUCTION

Guinea pigs have long been used for animal experimentation because they are small, tame animals that are easy to control. Detailed information related to the general structure of the guinea pig is available,^{1,2} but in spite of numerous otologic studies carried out on this animal, limited information about the structure of its middle ear and eustachian tube is available. Asarch et al³ and Sehitoglu et al⁴ have described the guinea pig middle ear and its contents.

In our study, we investigated the temporal bone, eustachian tube, and inner ear anatomy in addition to the anatomy of the middle ear and its contents. Differences and similarities between human and guinea pig ears are assessed. We believe that this study will be a helpful guide for investigations that might be carried out on the ossicles, facial nerve, eustachian tube, mastoid cells, and inner ear of guinea pigs.

MATERIALS AND METHODS

We studied 18 healthy guinea pigs, weighing 500 to 650 g, from the Central Institute of Hygiene. After painless decapitation and skinning, the temporal bones were exposed and all soft tissues were removed. The structures neighboring the temporal bone were identified (Fig 1A,B). With use of a dissection microscope, each step was photographed. We started the dissection by removing the lateral bony plates of the "squamosal" and "mastoidlike process" portions of the temporal bone, thus revealing the epitympanic and retrotympanic air cell systems (Fig 1C,D). Second, the tympanic ring was removed and the lateral portion of the external ear canal was drilled. Then the

eardrum was dissected to expose the tympanic cavity. The bony lamina hiding the malleoincudal complex was removed to expose the relation of the malleoincudal complex to the epitympanic cavity, the lateral semicircular canal, and the superior semicircular canal, as well as the relation with the stapes and the other structures of the tympanum (Fig 2). After the malleoincudal complex was taken away, the wall of the bony facial canal was removed to reveal the course of the nerve within the temporal bone (Fig 3). In an attempt to show the inner ear structures, the basal parts of the cochlea and the bony ridge between the oval and round windows were dissected away (Fig 4). The course of the eustachian tube was followed by dissecting from the tympanic cavity toward the nasopharyngeal opening (Fig 5). Finally, the temporal bone as a whole was reflected laterally from the skull to reveal its medial aspect and the various structures of this bone, including the entry of the nerves (Fig 6).

RESULTS

Temporal Bone. The temporal bone of the guinea pig lies posterior and inferior to the squamosal bone. In general the guinea pig temporal bone consists of a mastoidlike process, a tympanic bulla, a tympanic ring, a petrosal segment, and a poorly developed squamosal portion that is covered by the posterior projection (tympanic hook) of the squamosal bone. Posterior to the bulla and inferior to the mastoidlike process lies a bony projection of occipital bone. The tympanic ring that forms the bony external ear canal is fused firmly to the lateral aspect of the bulla, but leaves an opening in the inferior aspect. This opening is obliterated by soft tissue that is in continuity with

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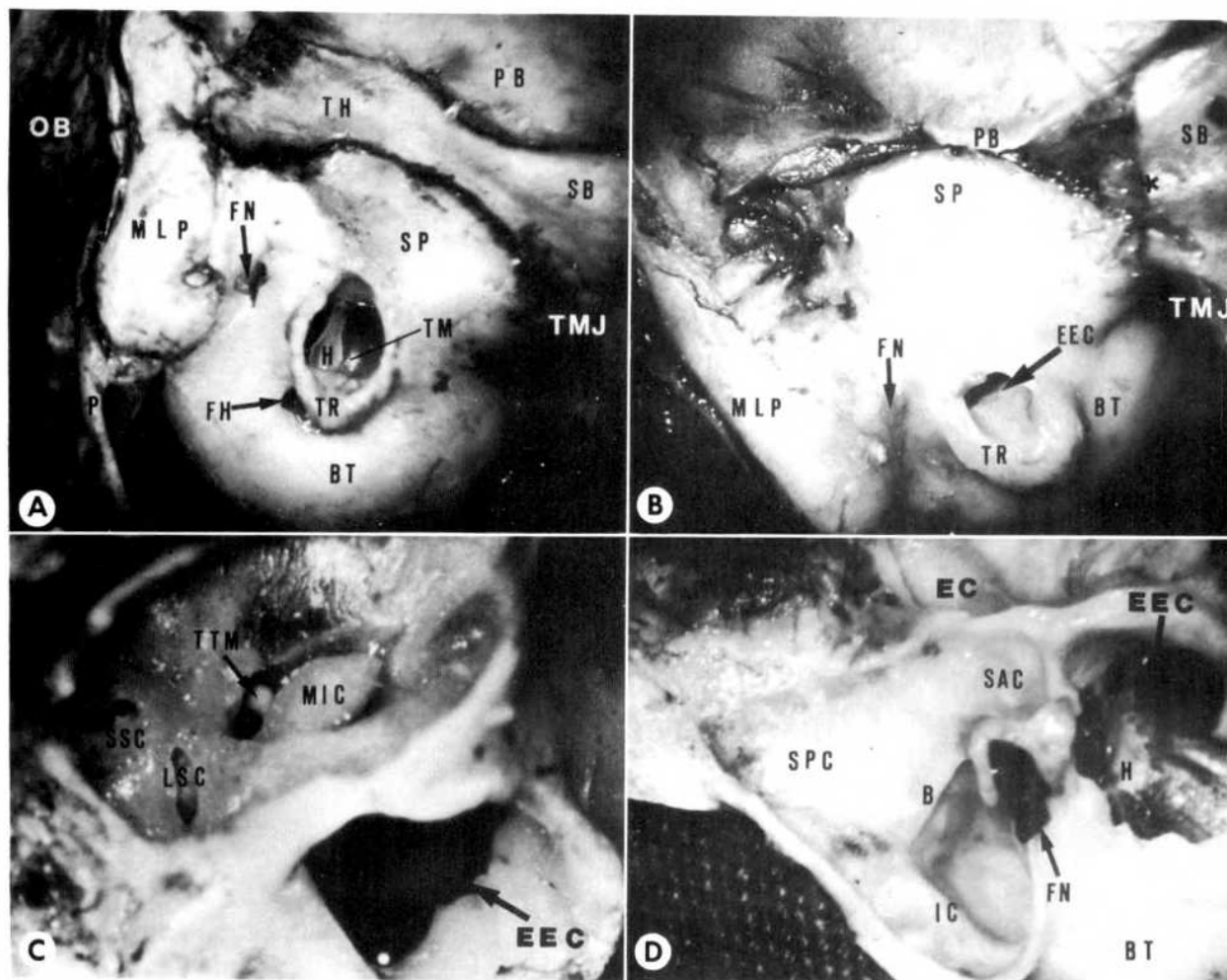


Fig 1. Photographs taken through dissection microscope, showing A) right temporal bone of guinea pig, B) temporal bone after removal of tympanic hook (TH) of squamosal bone (SB), C) epitympanic cell (EC) and its contents after removal of lateral wall of squamosal portion (SP), and D) retrotympanic cell and its subspaces after removal of lateral wall of mastoidlike process (MLP) and tympanic ring (TR). B — branch of facial nerve, BT — tympanic bulla, EEC — external ear canal, FH — foramen of Huschke, FN — exit point of facial nerve (stained in D), H — handle of malleoincudal complex (MIC), IC — inferior part of retrotympanic cell, LSC — lateral semicircular canal, OB — occipital bone, P — bony process of occipital bone, PB — parietal bone, SAC and SPC — superoanterior and superoposterior parts of retrotympanic cell, respectively, SSC — superior semicircular canal, TM — tympanic membrane, TMJ — temporomandibular joint, TTM — tensor tympani muscle, asterisk — removed edge of tympanic hook.

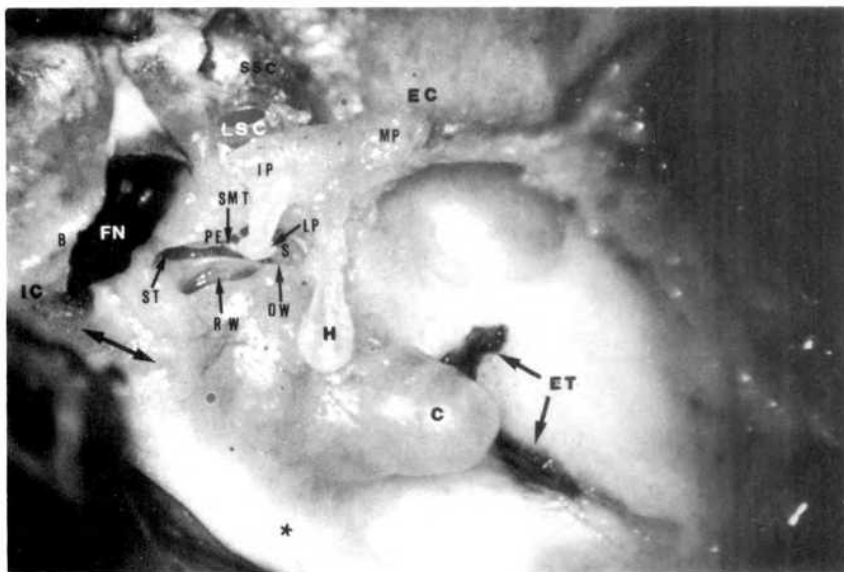
the ear canal skin (Fig 1A).

Air Cell System. The temporal air cell system of the guinea pig is divided into two groups: epitympanic and retrotympanic cells. The epitympanic cell communicates with the bulla by a hiatus that contains the anterior portion of the malleoincudal complex. Through this hiatus the tensor tympani muscle with its bony canal is visible. The prominences of the superior and lateral semicircular canals are seen at the posteromedial wall of this space (Fig 1C). The retrotympanic cell could be described as three subspaces: inferior, superoposterior, and superoanterior (Fig 1D). The inferior subspace directly communicates with the inferoposterior bulla (Fig 2). The superoposterior part is separated from the inferior one by a bony ridge that contains a branch of the facial

nerve. The superoanterior part opens to the superoposterior cell. Removing the medial wall of this cell reveals the space that contains the incudal part of the malleoincudal complex; this space (attic) opens to the superoposterior part of the bulla.

Tympanic Bulla. The tympanic bulla is a semi-spherical cavity that is bounded by the tympanic ring laterally, the mastoidlike process posterolaterally, and the epitympanic cavity superiorly. The tympanic membrane, which is extremely thin and devoid of a fibrous layer, lies in a smooth groove formed by the lateral wall of the bulla (Fig 1A). The diameter of the tympanic sulcus and thus the tympanic membrane is much greater than the tympanic ring's diameter, so that a hidden space is formed anterior to the tympanic membrane.

Fig 2. Photograph taken through dissection microscope, showing tympanic space and its contents viewed from lateral side after removal of tympanic ring, tympanic membrane, lateral wall of tympanic bulla, squamosal portion, and mastoidlike process, and bony lamina hiding ossicular complex between epitympanic cell (EC) and tympanic cavity. C — cochlea, ET — eustachian tube (stained), FN — facial nerve (stained), IP — incudal part of MIC, LP — lenticular process of MIC, LSC — lateral semicircular canal (opened), MP — malleolar part of MIC, OW — oval window, PE — pyramidal eminence, RW — round window, S — stapes, SMT — stapedius muscle tendon, ST — sinus tympani, asterisk — inferoposterior part of bulla (tympanic cavity), two-way arrow — passage between inferior part of retrotympenic cell (IC) and inferoposterior part of bulla. Other abbreviations as in Fig 1.



The most prominent structure in the bulla is the cochlea, which projects mediolaterally, posteroanteriorly, and to a lesser degree superoinferiorly. The

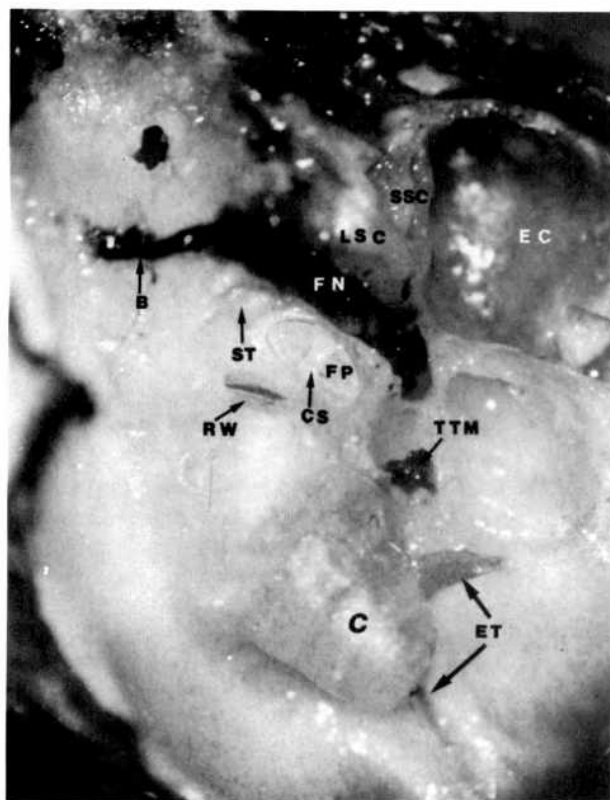


Fig 3. Photograph taken through dissection microscope showing medial wall of tympanic cavity after removal of ossicles and lateral bony wall of facial nerve in addition to structures removed in Fig 2. B — branch of facial nerve (stained), C — cochlea, CS — crista stapedis, EC — epitympanic cell, ET — eustachian tube (stained), FN — facial nerve (stained), FP — footplate of stapes, LSC — lateral semicircular canal, RW — round window, SSC — superior semicircular canal, ST — sinus tympani, TTM — tensor tympani muscle (stained).

apical turns of the cochlea partially hide the hiatus of the eustachian tube, which lies in the anteromedial wall of the bulla (Figs 2 and 3). The oval window sealed with the stapes; the round window; the pyramidal eminence; the tendon of the stapedius muscle; the sinus tympani; the semicircular canal; and the tensor tympani muscle are visible at the superior part of the medial wall (Figs 2, 3, and 7A). The inferior part of the bulla is smooth and covered by a thin mucosa and extends posteriorly in a trough shape to communicate with the inferior retrotympenic space (Fig 2).

Ossicles. In the guinea pig, the head of the malleus and the body of the incus are fused, forming a malleo-incudal complex. The fusion line of the malleo-incudal complex between the malleolar part and the incudal part can be identified at a high magnification as a shallow groove (Figs 2, 7, and 8). As in humans, the handle of the malleo-incudal complex is located within the two layers of the tympanic membrane (Fig 1A), and the long process of the malleo-incudal complex articulates with the stapes via the lenticular process (Figs 2, 7A, and 8). The stapes of the guinea pig is almost identical to that of the human with the exception of the presence of the crista stapedis, a bony bridge between the crura of the stapes above the footplate (Figs 3 and 7). There are two muscles: the stapedius muscle, which lies in a bony canal (pyramidal eminence) just beneath the facial canal and inserts into the neck of the stapes (Figs 2, 7A, and 8); and the tensor tympani muscle, which lies in a bony groove (the hiatus), its tendon inserting into the neck of the handle (Figs 1C, 4, 7A, and 8).

Eustachian Tube. This is a J-shaped structure that lies in a bony hiatus at the anteromedial aspect of the bulla and leaves the bulla to reach the nasopharynx

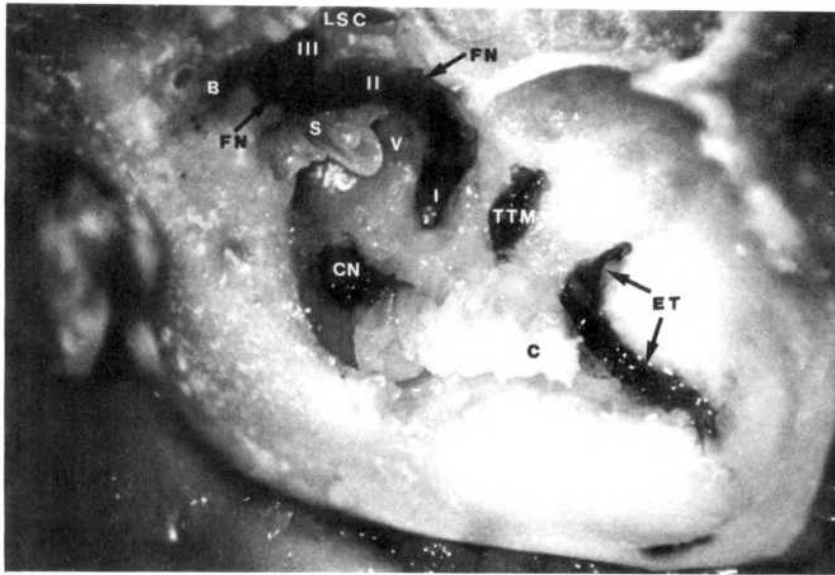


Fig 4. Photograph taken through dissection microscope, showing medial wall of tympanic cavity after removal of footplate of stapes, cochlea, and bony canal of facial nerve along its whole intratympanic course in addition to structures removed in Fig 3. B — Branch of facial nerve (stained), C — osseous spiral lamina of cochlea, CN — cochlear nerve (stained), ET — eustachian tube, FN — facial nerve (stained), I, II, III — first, second, and third parts of FN, respectively, LSC — lateral semicircular canal, S — stapes, TTM — tensor tympani muscle, V — vestibule.

(Figs 2-5). The entire guinea pig eustachian tube, unlike that of the human, is made of cartilage. It is crescent-shaped in cross section and lies in a bony

groove that extends almost to the nasopharyngeal opening (Fig 4).

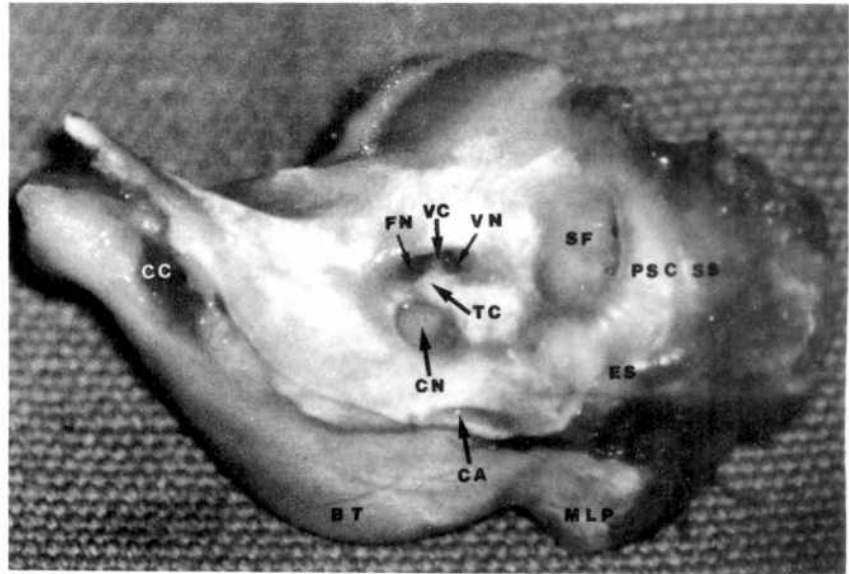


Fig 5. Photograph of eustachian tube from tympanic cavity to nasopharyngeal opening, taken through dissection microscope after removal of medial and inferior wall of tympanic cavity, cochlea, and ossicles. CN — cochlear nerve, EP — extratympanic part of ET, ET — eustachian tube, FN — facial nerve, IP — intratympanic part of ET, N — nasopharyngeal opening of ET.

Facial Nerve. After leaving the brain stem, the facial nerve enters the temporal bone through a foramen that is located superior to the entry of the cochlear nerve and anterior to the vestibular nerve. In the guinea pig, the acoustic-vestibular-facial nerve bundles enter the temporal bone directly, and no distinct internal meatus is found, but a transverse and a vertical bony crest are clearly observed (Fig 6). After a 1- to 2-mm course in the petrous portion, the facial nerve turns in an upward direction at the medial aspect of the basal turn of the cochlea, and connects with the middle ear portion of the nerve, which courses horizontally and posteriorly. Here, it courses near the oval window in an eyebrow fashion (Figs 3 and 4). Then it makes a third junction, from which it courses laterally, giving off the chorda tympani nerve (Fig 7), and it leaves the temporal bone via a foramen located posterosuperior to the tympanic ring. Just after the third junction, a tiny branch of the nerve, in a bony crista separating the retrotympenic air cells, is apparent, coursing in a posterior direction (Figs 1A,B,D and 2).

Inner Ear. The inner ear of the guinea pig consists of the cochlea (Figs 2 and 3), semicircular canals (Figs 1C, 2, and 3), and vestibule (Fig 4). The cochlea has 3.25 turns and projects into the bulla, just behind the eardrum and the handle of the malleoincudal complex. The round window lies in a horizontal plane that is perpendicular to the oval window plane (Figs 2, 3, and 7A). The prominences of the lateral and superior semicircular canals are visible in the epitympenic space (Fig 1C). The lateral semicircular canal lies just above the facial canal (Fig 3) and anteriorly

Fig 6. Photograph taken through dissection microscope, showing posterior aspect of temporal bone. BT — posterior aspect of tympanic bulla, CA — cochlear aqueduct, CC — carotid canal, CN — exit point of cochlear nerve, ES — bony niche overlying endolymphatic sac, FN — entry of facial nerve, MLP — posterior aspect of inferior part of mastoidlike process, PSC — posterior semicircular canal, SF — subarcuate fossa, SS — groove of sigmoid sinus, VC — vertical crest, TC — transverse crest, VN — exit point of vestibular nerve.



communicates with the superior semicircular canal, which turns superiorly and posteriorly to meet the posterior semicircular canal just behind the vestibular nerve entry (Fig 6). Two trough-shaped impressions resembling the utricle and the saccule, as in the human, could be seen. From the posterior aspect of the temporal bone, the bony niche of the endolymphatic sac could easily be seen (Fig 6).

DISCUSSION

As noted by others,^{3,4} the guinea pig temporal bone and its contents are similar to those of the human, but there are some exceptions that become important for experimental studies.

1. The dimensions of the eardrum and tympanic

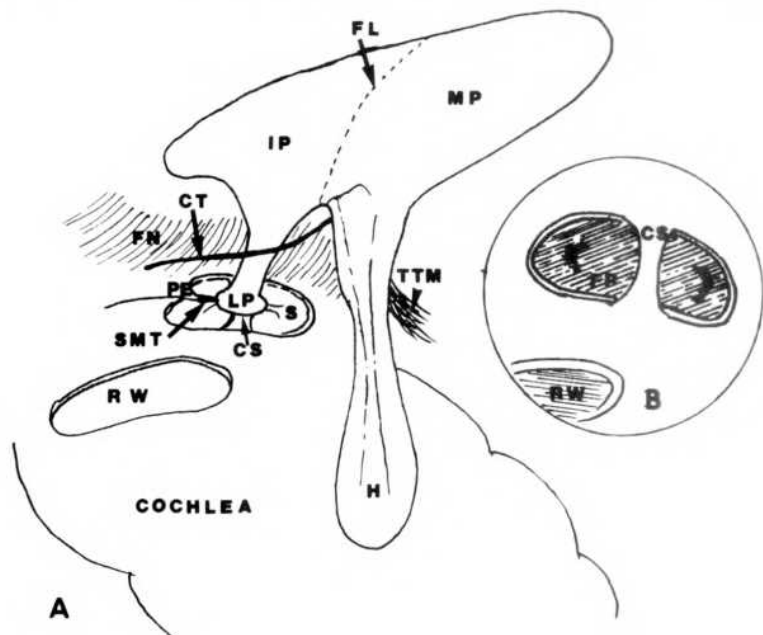
ring are greater in the guinea pig than in the human in relation to the temporal bone dimensions, and, unlike in the human and rat,⁵ the tympanic membrane of the guinea pig is devoid of a pars flaccida.

2. A foramen resembling Huschke's foramen (an opening found in the first 2 years of life in humans⁶) is observed in the guinea pig (Fig 1A).

3. The air cell system is simplified and consists of mainly four large cells, without fine trabeculations as in the human (Fig 1C,D).

4. The guinea pig temporal bone contains a very large and smooth hypotympanum, known as the bulla (Fig 1A). This was emphasized by Asarch et al³ and Sehitoglu et al.⁴ Hellstrom et al⁵ described a similar

Fig 7. Schematic view of A) structures on medial wall of tympanic cavity and B) footplate of stapes (FP) and crista stapedis (CS). CT — chorda tympani, FL — fusion line between malleolar part (MP) and incudal part (IP) of malleoincudal complex (MIC), FN — facial nerve in its bony canal, H — handle of MIC, LP — lenticular process of MIC, PE — pyramidal eminence, RW — round window, S — stapes, SMT — stapedius muscle tendon, TTM — tensor tympani muscle.



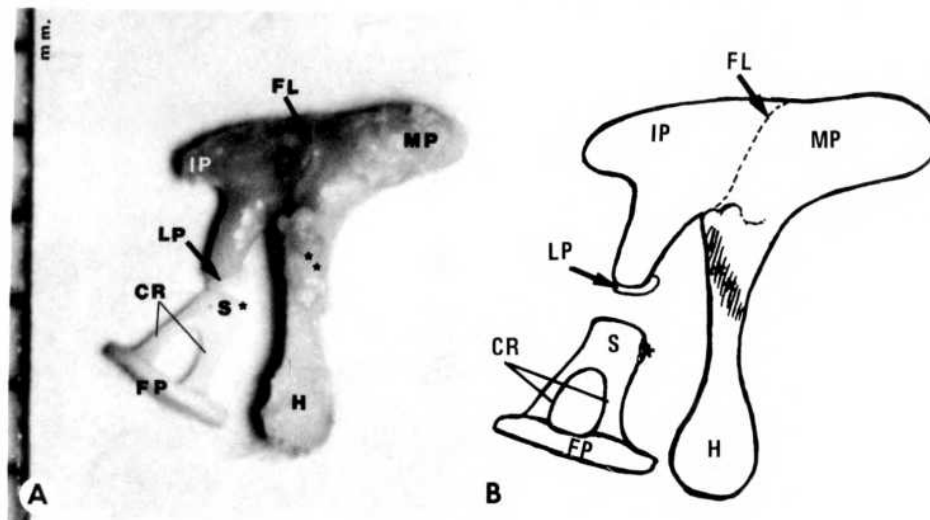


Fig 8. Ossicles. A) Photograph. B) Drawing. CR — crura of stapes, FP — footplate, S — capitulum of stapes, single asterisk — attachment of stapedius muscle, double asterisk — attachment of tensor tympani muscle. Other abbreviations as in Fig 7.

hypotympanum in rats.

5. As noted in the previous studies,^{3,4} there are two ossicles: the malleo-incudal complex and the stapes (Fig 8). In rats, the ossicular chain is almost identical to that in humans.⁵

6. At the base of the stapes, the crista stapedis is persistent (Figs 3 and 7), as in the human embryo.⁶ This bony ridge is observed in chinchillas,⁷ but not in rats.⁵

7. The cochlea projects well into the bulla (Figs 2 and 3).

8. The entire eustachian tube is cartilaginous.

9. The exit of the facial nerve is in a posterosuperior position between the tympanic ring and the mastoid-like process (Fig 1A,B).

10. The cochlea consists of 3.25 turns.

11. The guinea pig lacks an internal auditory meatus

(Fig 6).

Hellstrom et al⁵ emphasized that the ventilatory and drainage scheme of the rat middle ear is similar to that of the human, because of the communications among the eustachian tube, the attic region, and the middle ear cavities, and so they suggested that the rat middle ear might have advantages compared with the guinea pig and chinchilla, especially in tubal blockade studies.

In conclusion, the temporal bone and ear structures of the guinea pig are good models for the human ear, and they can be manipulated with great ease if differences and similarities are known.

For experimental studies, the histologic characteristics of middle ear mucosa are important, in addition to the architecture of the middle ear. Therefore, one must select the type of animal carefully, considering the aim of the study and the anatomic properties of the species.

ACKNOWLEDGMENT — We are grateful for the help given by G. Osmanlioglu, MD, from the Central Institute of Hygiene.

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IMAGING CASE STUDY OF THE MONTH

ANEURYSM OF THE ANTERIOR INFERIOR CEREBELLAR ARTERY PRODUCING HEARING LOSS

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CASE REPORT

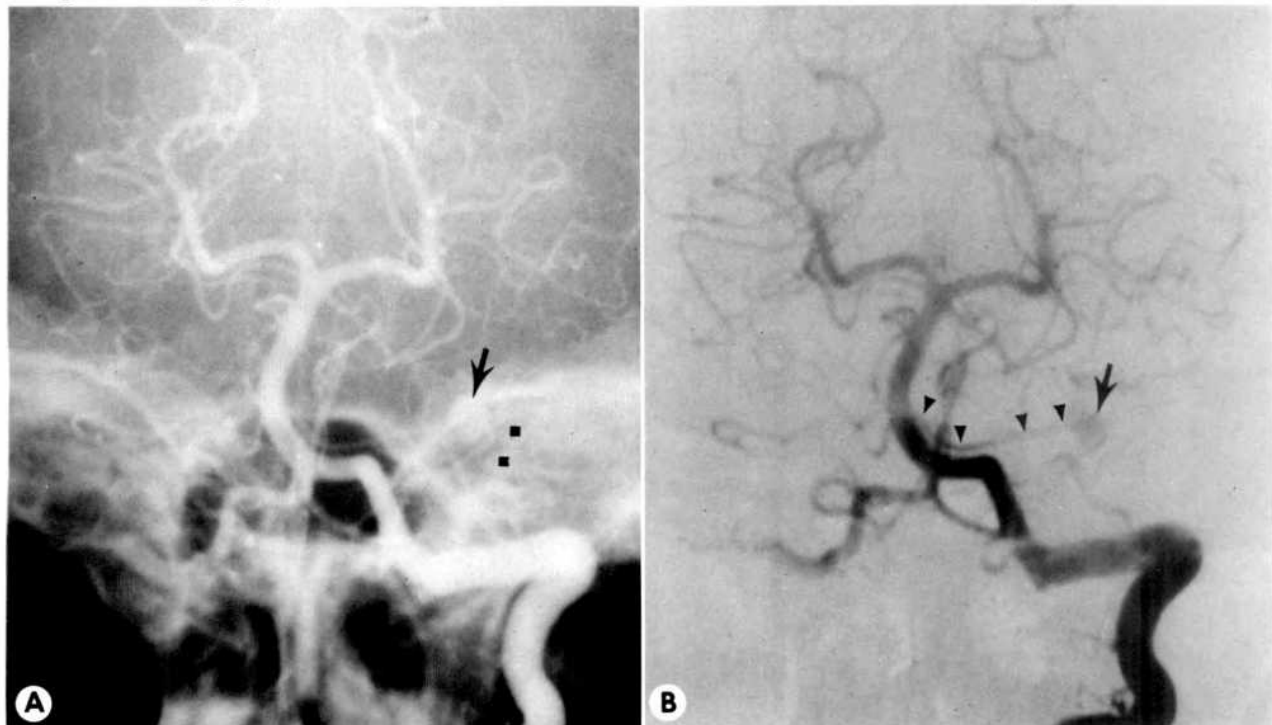
A 25-year-old man presented with left-sided hearing loss, tinnitus, vertigo, and nausea of 1 day's duration. Physical examination and audiometric testing revealed a profound sensorineural hearing loss on the left and normal hearing on the right. The remainder of the findings on head and neck examination were unremarkable. The patient's vertigo and nausea subsided; however, his left-sided hearing loss was unchanged at 1-week follow-up. Computed tomography of the temporal bones revealed no apparent abnormalities.

Three months later the patient presented with a 3-day history of headache, vomiting, and stiff neck. Physical examination was remarkable for nuchal rigidity and an unchanged left-sided deafness. Computed tomography showed evidence of hemor-

rhage into the fourth ventricle, and findings on lumbar puncture were consistent with subarachnoid hemorrhage (SAH). Cerebral angiography revealed a 6- to 7-mm saccular aneurysm arising from a loop of the left anterior inferior cerebellar artery (AICA) at the porus acusticus (see Figure).

The following day the patient underwent a left posterior fossa craniotomy and surgical clipping of the aneurysm. During the operation cranial nerves VII and VIII were observed to be stretching around a large blue mass located at the internal acoustic meatus. There also appeared to be evidence of fresh clot and scarring.

Postoperatively the patient's hearing loss was unchanged. A 1-month follow-up cerebral angiogram revealed no evidence of aneurysm.



Left vertebral angiograms. A) Showing 6-mm aneurysm arising from left anterior inferior cerebellar artery (arrow). Dots — porus acusticus. B) Subtraction view of A. Arrowheads — anterior inferior cerebellar artery, arrow — aneurysm.

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DISCUSSION

Intracranial aneurysms occur with a prevalence of approximately 10% in the posterior fossa. The majority of these aneurysms arise near the bifurcation of the basilar, vertebral, or posterior inferior cerebellar arteries.¹ A peripheral AICA aneurysm is extremely rare. Approximately 41 cases, including this one, have appeared in the world literature.²

The majority of these peripheral AICA aneurysms originate from arterial loops near the internal auditory meatus. Naidich et al³ describe the typical AICA as originating from the basilar artery and bifurcating into the rostralateral and caudomedial arteries. The rostralateral artery courses superolaterally to loop around the seventh and eighth nerves near the internal acoustic meatus. Frequently this loop gives rise to the internal auditory artery. This general location is the usual site of aneurysmal development.

Common presenting signs and symptoms of these aneurysms are identical to those of cerebellopontine angle tumors because of their location. In fact, it is not uncommon for these lesions to be preoperatively diagnosed as acoustic neuromas.¹ Many patients also present with more acute symptoms suggestive of SAH.

According to a comparative study of 33 operative cases by Kiya et al,² these lesions occur with a 2:1 female preponderance and a mean age of 47.6 years; the occurrence between cerebral hemispheres

is roughly equivalent; and clinical manifestations of SAH present in 76% of cases. They described the most common signs to be eighth nerve paresis (85%), seventh nerve paresis (52%), nystagmus (36%), and cerebellar signs (24%).

The management of these lesions is predominantly surgical. Operative procedures have been performed in 38 of the 41 known cases. The procedure of choice is aneurysm clipping. The variability of the AICA anatomy and aneurysms extending into the internal acoustic meatus often prevent proper clipping procedures. In these cases aneurysm trapping or wrapping or AICA obliteration has been performed.²

Postoperative improvement of symptoms is highly variable. In the comparative study of Kiya et al,² 35% of patients with eighth nerve paresis improved, while another 35% of patients reported deterioration. Seventh nerve paresis showed improvement in 69% of cases.

Although the acoustic neuroma accounts for 90% of cerebellopontine angle syndromes, peripheral AICA aneurysms must be included in the differential diagnosis, especially if symptoms of SAH are present. These aneurysms are thought to manifest symptoms by way of compressive forces or disturbances of flow in the internal auditory artery.¹ Surgical clipping is the treatment of choice. Postoperative improvement is variable and suggests that perhaps eighth nerve paresis is less reversible than seventh nerve paresis.²

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IMAGING CASE STUDY OF THE MONTH

BONE SCAN DIAGNOSIS OF MASKED MASTOIDITIS

FERIT TOVI, MD

ALBERT GATOT, MD

BEER-SHEVA, ISRAEL

Inflammation of the mucosal lining of the mastoid air cells (mastoiditis) is a common condition. It occurs in all categories of otitis media because the middle ear cleft is a contiguous structure. Acute mastoiditis is a term coined to define osteitis in the partitions of the mastoid air cells. It may occur in the coalescent phase of acute otitis media and in chronic middle ear infections.^{1,2} In both conditions the clinical picture is usually stormy. Another, atypical form of mastoiditis consists of a low-grade bone infection following an insidious course until the dramatic occurrence of intracranial or intratemporal complications.^{3,4} Sometimes the disease is recognized only after the development of these complications. Early recognition is often difficult because both clinical and radiographic features are covert³; the disease is therefore frequently overlooked. The diagnosis of masked mastoiditis is suggested by signs and symptoms of acute mastoiditis with a virtually normal middle ear, the latter having responded to prior antibiotics. Sometimes diagnosis can be difficult to establish. The purpose of this report is to describe the role of bone scanning in turning the assumptive diagnosis into a confirmed one.

CASE STUDY

A 12-year-old boy was referred by the family physician because of left retroauricular pain, fever, and vomiting. He had a history of recurrent bouts of otitis media for which ventilation tubes had been previously inserted. Two months prior to the present admission he had been hospitalized because of similar complaints and treated by antibiotics.

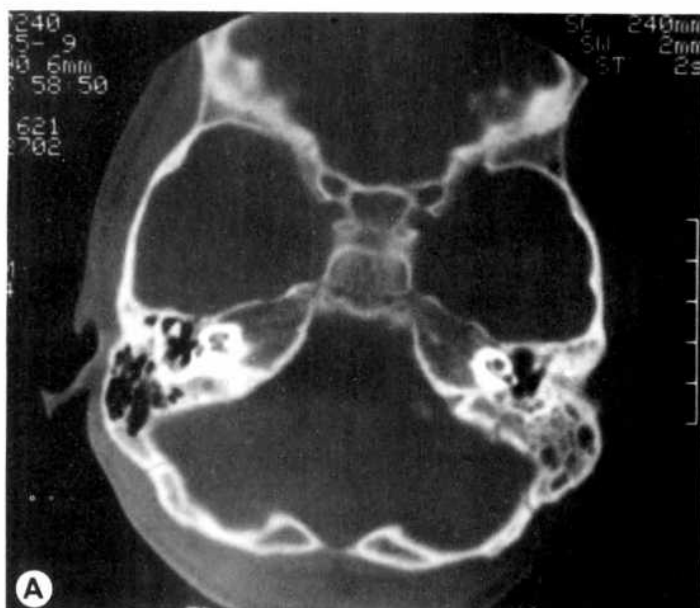
On admission he was febrile (38°C). At physical examination the eardrum was found to be thickened. There was no discharge through the ventilation tube. The posterolateral wall of the ear canal was sagging and the postauricular area was mildly swollen and tender. The rest of the otorhinolaryngologic examination findings were normal and no neurologic deficit was detected. A routine blood cell count showed 11,000 white cells per cubic millimeter. An audiologic examination revealed a 50-dB air-bone gap in the left ear. Computed tomography (see Figure, A) of the temporal bone showed clouding of the left mastoid cells without bony changes.

The middle ear appeared well aerated. Tissue swelling in the left postauricular area was present. A triphasic bone scan performed with technetium methylene diphosphonate (Tc-99 MDP) showed a mild activity of the isotope agent, at the blood pool phase, in the left mastoid area (see Figure, B). In the delayed phase, a moderate increase in the uptake of the isotope was detected in the same area (see Figure, C). A gallium-67 citrate (Ga-67) scan showed concentration of the isotope agent in the left temporal area. Osteitis was thereupon diagnosed. Intravenous cefuroxime sodium 100 mg/kg per day was initiated. At mastoidectomy the bone cortex was intact. Granulation tissue of the antrum and mesotympanum was cleaned and infected bony tissue was removed. The articular process of the incus was found to be necrotic. No pus was detected within the mastoid air cells. Intact wall tympanomastoidectomy was accomplished with incudostapediopexy and the reinforcement of the posterior aspect of the eardrum with a periosteal graft. The tympanostomy tube was preserved. The postoperative period was uneventful. Histologic examination of the removed mastoidectomy material showed chronic subepithelial inflammatory changes and osteitis. At follow-up the patient remained free of symptoms and a repeat Ga-67 scan was negative.

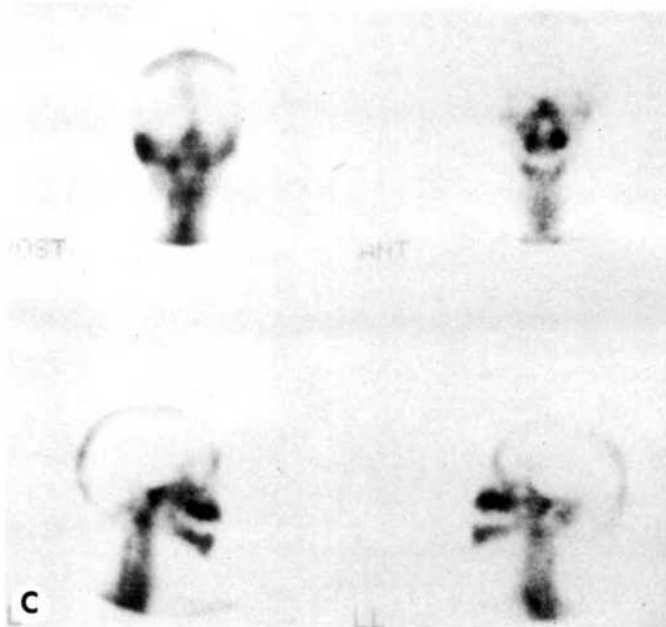
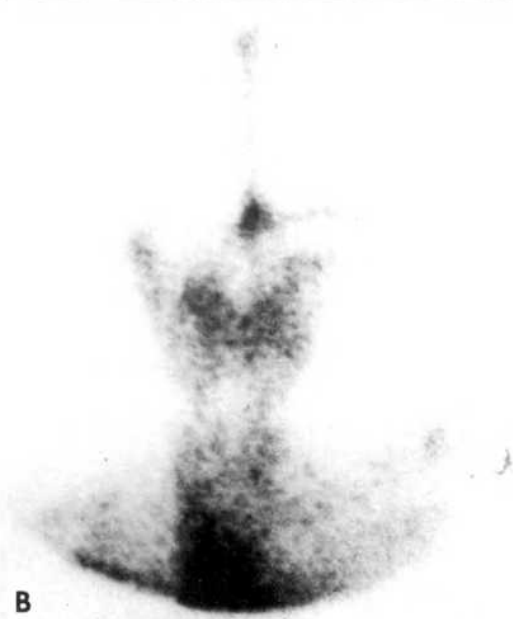
DISCUSSION

The term masked mastoiditis refers to irreversible mucosal and bony changes within the mastoid and a middle ear with no particular abnormality.³ The entity has been recognized since the introduction of antibiotics. This atypical mastoiditis, known also as silent otitis media, otitis-prone condition, or latent mastoiditis,⁴ occurs as a consequence of inadequate antimicrobial therapy in cases of acute otitis media.⁵ An insufficient course of therapy may provide a relief of the clinical symptoms and the middle ear may become aerated by the return of eustachian tube function. Yet, because of the obstruction of the tympanic diaphragm⁶ by mucosal swelling, polypoid mucosa, or granulation tissue, a complete or incomplete separation of the tubotympanic cavity from the mastoid air cell system occurs. Accordingly, the latter remains unaerated and the local infectious mucosal process progresses into osteitis. Be-

From the Department of Otorhinolaryngology, Soroka Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.



Masked mastoiditis. A) Axial computed tomogram of temporal bone shows occlusion of left external ear canal, well-aerated middle ear, and clouding of mastoid air cells without bony changes. B) Posterior view of blood pool phase of bone scan demonstrates mild increase in isotope activity, laterally in left temporal bone. C) Delayed phase of bone scan images in posterior, anterior, and lateral display demonstrates moderate increase in technetium methylene diphosphonate uptake in left mastoid.



cause of the colonizing flora in this anaerobic condition, the developing bone infection is of a low grade³ and the clinical features are not overt as are those of acute mastoiditis. Pain is minimal and fever is not high. The most striking aspect is that otoscopic findings do not reflect the serious nature of the bone-eroding mastoid disease. The eardrum may appear intact^{3,4,7} or may show a thickening or a mild inflammatory reaction. Even in the presence of a perforation, the middle ear lining does not show particular changes.⁸ Diverse intracranial, intratemporal, and at times distant complications may develop in these apparently innocent ears.^{3,4,8,9}

Plain x-ray film or computed tomographic scans in this case usually show only clouding of the mastoid air cells,^{3,8} corresponding to the thickening of the subepithelial layer in middle ear cleft infections.

The absence of marked bony changes in radiographic investigation is most probably due to low-grade osteitis in which the bone destruction and demineralization are not as overt as those occurring in acute mastoiditis. For clear radiographic diagnosis of bone destruction, a large amount of bone matrix (30% to 50%) should have been destroyed or demineralized.¹⁰ However, functional images provided by bone scan can indicate the osteoblastic response to an osteolytic process even when the marginating hypermineralization is low (about 5%).¹¹ Bone scan results are both quantitative and qualitative. This scan is highly sensitive but not specific. The isotope agent Tc-99 MDP concentrates in areas of osteogenesis; hence, it depicts the local metabolic bone activity secondary to infection, fracture, osteoblastic metastases, Paget's disease, or meningioma.¹⁰ When the nature of the insult is not clear,

a positive Ga-67 scan may suggest an active infectious inflammatory process. However, Ga-67 positivity is not specific for infection; it can also occur in tumors.^{12,13} Multiple factors contribute to the accumulation of Ga-67 in inflammatory lesions.¹³ An adequate blood supply is essential. Capillaries with increased permeability, in the area of inflammation, deliver this isotope in the form of transferrin-Ga-67 complex. At the same site some Ga-67 is also taken up by leukocytes and bacteria. In addition, the isotope may also bind to lactoferrin and bacterial siderophores. Accordingly, sequential use of Tc-99 MDP and Ga-67 scans brings a more precise diagnosis of active bone infection. In our case, the infectious inflammatory nature of the ear disease was clinically obvious. The Ga-67 scan was

performed in order to confirm it and also to establish a baseline for follow-up purposes.

The mild increase in Tc-99 MDP activity at the blood pool phase, together with the moderate uptake of the isotope in the temporal bone at the delayed phase of the bone scan, was consistent with a low-grade bone infection. This was confirmed histologically.

A high index of suspicion is necessary for the diagnosis of masked mastoiditis.³ A bone scan demonstrating the bone-invading nature of the mastoid infection is of paramount importance in the definitive diagnosis, as well as in the prompt treatment of the disease before catastrophic consequences develop.

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PATHOLOGY CONSULTATION

NEUROENDOCRINE TUMORS OF LARYNX

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HOUSTON, TEXAS

Neuroendocrine neoplasms of the larynx have either an epithelial or a neural basis. The former are more numerous and are classified as typical or atypical carcinoids and small cell neuroendocrine carcinomas. Paraganglioma is the sole type of neural neuroendocrine neoplasm. There is a significant worsening of prognosis from typical carcinoid to small cell neuroendocrine carcinoma, with the latter having a dismal 5-year survival rate regardless of therapy. Paragangliomas are the most benign of laryngeal neuroendocrine neoplasms, but their clinical behavior may not be predictable on the basis of their histologic appearance.

After the publication of approximately 400 cases and an accompanying evolution of nomenclature and classifications of neuroendocrine neoplasms of the larynx, their clinicopathologic status seems defined, at least for now. Table 1 presents the two categories based on their proposed generative tissues, epithelial and paraganglionic, and the recommended histopathologic classification.^{1,2} Numerous markers justify the encompassing rubric of neuroendocrine for these neoplasms. These include an argyrophilia of cytoplasmic granules; immunoreactivity with antibodies against chromogranin, neuron-specific enolase, neurofilament protein, Leu-7, calcitonin, and synaptophysin; electron optic findings of membrane-bound dense-core granules; occasional association with paraneoplastic syndromes; and the rarely seen extracellular elevations of peptides, amines, and hormones.¹

CARCINOIDS OF LARYNX

In terms of the published reports, carcinoids are the most numerous of the neuroendocrine tumors of the larynx. They exist in two types, typical and atypical, with the typical carcinoid being the least common of any laryngeal neuroendocrine tumor.³ They derive from uncommitted stem cells that are apparently most plentiful in the supraglottis, since that is the

region of predilection.

In a critical review of the world literature up to 1991 there were only 13 reported typical laryngeal carcinoids, making up about 3% of the entire spectrum of neuroendocrine neoplasms of the larynx.³ Typical carcinoids manifest an overwhelming male disposition; only 1 of the 13 patients was a woman. Nearly 200 cases of atypical carcinoid have been confidently identified in the literature by Woodruff and Senie.⁴ This neoplasm has a 3:1 predilection for males.

A histopathologic diagnosis of a typical laryngeal carcinoid is based on an organoid or ribbon architecture in which the cells are uniform and small (Fig 1A). The cells are typically devoid of cellular pleomorphism, mitoses, or necrosis. An atypical carcinoid differs by manifesting cellular pleomorphism, nuclear atypia, hyperchromatism, more than a rare division figure, and necrosis (Fig 1B). A variant of atypical carcinoid is medullary thyroid carcinoma-like (Fig 1C), even to displaying amyloid and immunocytochemically demonstrable calcitonin.^{5,6} Both typical and atypical forms, however, are usually nonfunctional.

There are considerable biologic differences between the two types of carcinoids. To date, none of the typical carcinoids of the larynx have had regional lymph node metastases at the time of clinical diagnosis, and overall, metastasis to lymph nodes is unusual.³ Four of the 13 reported tumors have manifested distant metastases, but only one patient has died of disease.³ Indeed, most patients with a typical carcinoid are alive and free of neoplasm after complete surgical removal of their neoplasms. This rather benign course

TABLE 1. NEUROENDOCRINE NEOPLASMS OF LARYNX

<i>Epithelial (Uncommitted Stem Cells)</i>	<i>Neural (Paraganglionic Cells)</i>
Carcinoids	Paragangliomas
Typical	
Atypical	
Small cell neuroendocrine carcinomas	

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

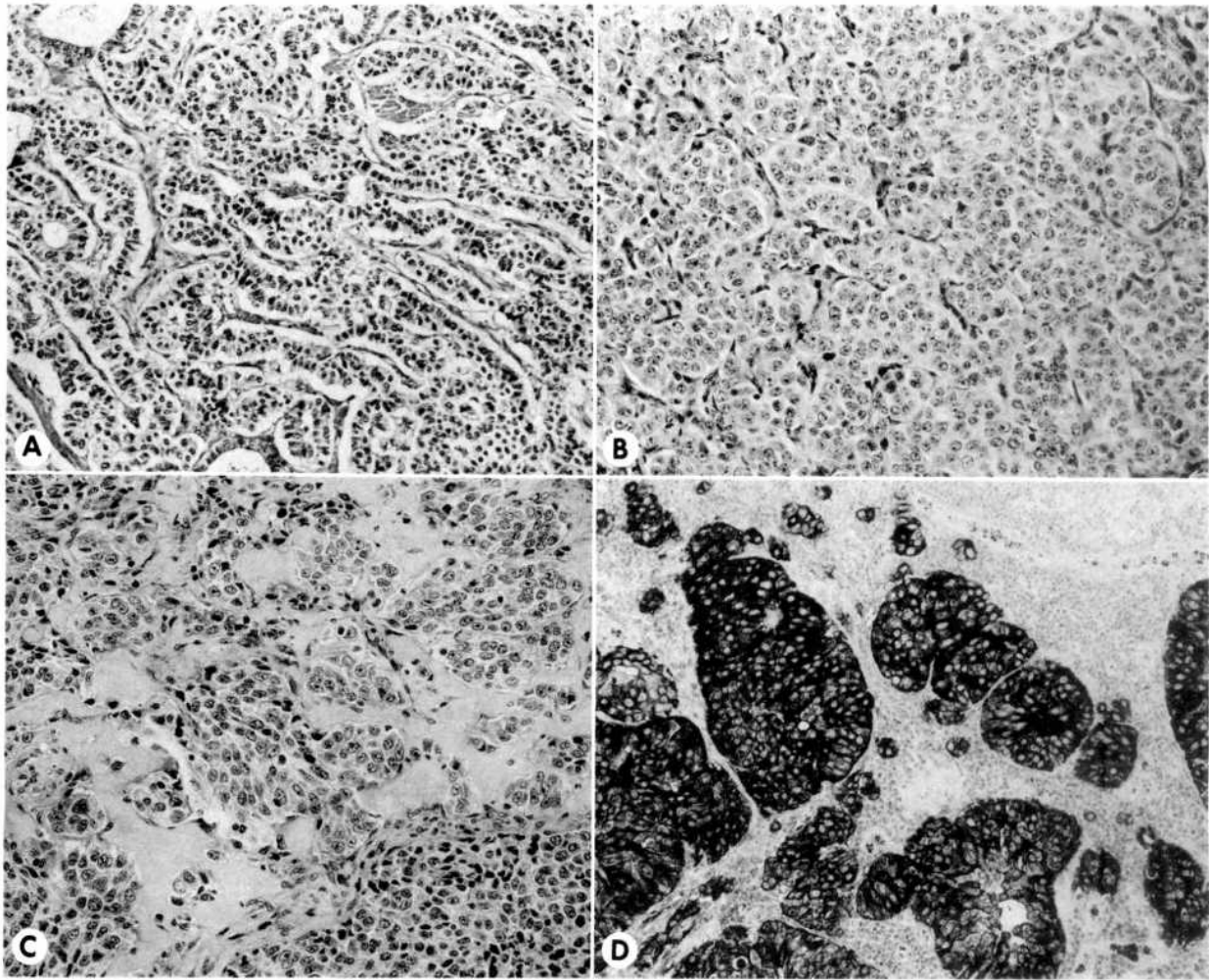


Fig 1. Carcinoid of larynx. A) Typical, with cords and ductular arrangement of uniform neuroendocrine cells (H & E, original x60). B) Atypical (H & E, original x120). Note degree of nuclear and cellular pleomorphism as compared with typical carcinoid in A. C) Atypical, with medullary (thyroid) carcinoma features (H & E, original x120). Note bands of amyloid intersecting cell groupings. D) Atypical, metastatic in cervical lymph node, showing immunoreaction for calcitonin (original x60).

is in contrast to that of an atypical carcinoid. Woodruff and Senie,⁴ in their survey of 127 cases, found metastases to the neck nodes in 43%, to skin and subcutaneous locations in 22%, and to distant sites in 44%. Nearly one half of a follow-up population of 119 patients died because of their neoplasms.⁴ The cumulative proportion surviving was 48% at 5 years and 30% at 10 years.⁴ Surgical resection was the principal therapeutic modality and survival rates were not changed by adjuvant irradiation.⁴

Both carcinoids display intracellular, neuroendocrine, immunocytochemical markers in a varying reactivity. Keratins are also reactive. It should be noted that the immunodetection of calcitonin (Fig 1D) is so common that it has come to be regarded as a very specific marker for an atypical carcinoid of the larynx, either in the primary or in its metastases.⁶ In addition to the intracellular calcitonin, the resemblance to medullary carcinoma of the thyroid is further accentuated by the presence of amyloid and,

at times, systemic manifestations of the calcitonin.^{5,6}

SMALL CELL NEUROENDOCRINE CARCINOMA

Approximately 125 cases of small cell neuroendocrine carcinoma of the larynx have been recorded in the literature since its first report in 1972.⁷ The carcinoma is estimated to account for about 0.5% of all primary laryngeal carcinomas and, like its neuroendocrine companions, has a predilection for men.⁷ The supraglottis has the highest incidence of involvement, but no part of the endolarynx is spared.⁸

Neuroendocrine carcinomas of the larynx share histologic features and descriptive subcategories with counterparts in the lungs, ie, oat cell, intermediate cell, and combined types. While we do not subscribe to these sometimes illusory subtypes, they are entrenched in the literature and hence require acknowledgment.^{7,9} The oat cell neuroendocrine carcinoma displays itself in sheets, cords, and ribbons of small,

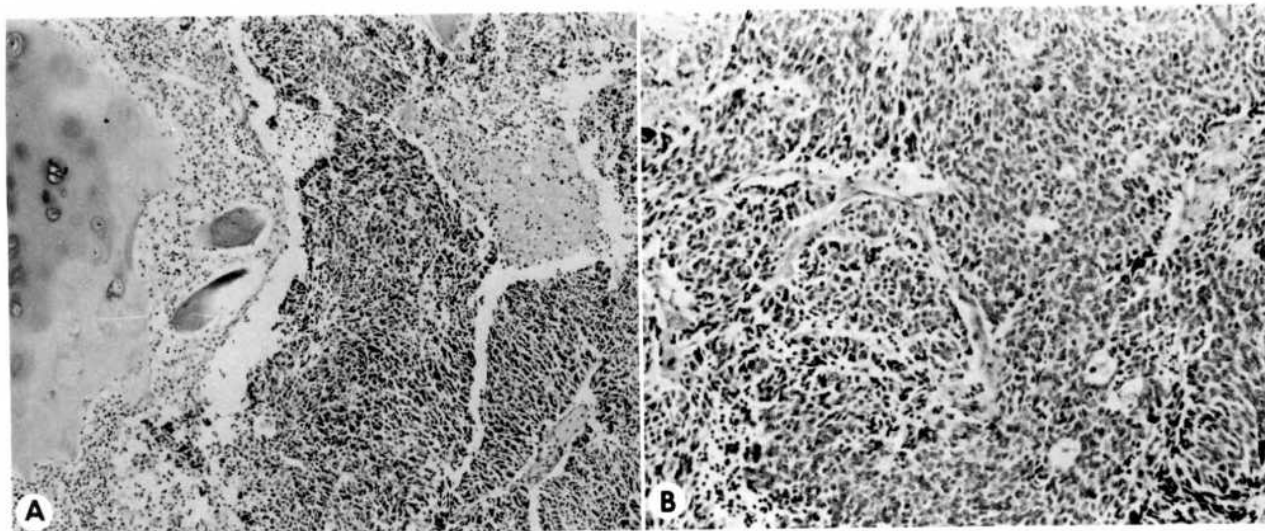


Fig 2. Small cell neuroendocrine carcinoma of larynx. A) Invading laryngeal cartilage (H & E, original x40). B) Composed of small undifferentiated cells (H & E, original x60).

hyperchromatic, undifferentiated cells with very scant cytoplasm (Fig 2). Necrosis, mitoses, and endovascular or lymphatic invasion are frequent. Substantiating a neuroendocrine differentiation, rosettes may occasionally be seen. The intermediate cell type has a slightly larger cell and more cytoplasm, and is more often variably shaped. As the designation indicates, combined forms show either an oat or intermediate cell type in company with squamous carcinoma, adenocarcinoma, or other classes of malignancy.⁷

Small cell neuroendocrine carcinoma of the larynx is an aggressive and lethal malignancy. Metastases to cervical lymph nodes coincident with discovery of the primary occur in nearly 50% of the patients.⁷ The prognosis is as poor as that for small cell carcinomas of the lung and it is unrelated to the size of the tumor. Gnepp et al¹⁰ indicate that three quarters of their study population died because of the carcinoma, usually with disseminated metastases and with an average survival of 9.8 months. There is a dismal 5% 5-year survival.⁷ These data reflect the treatment-resistant nature of the carcinoma. Ablative surgery is usually not an option because of the high metastatic rate.⁷ Combination therapy, chemotherapy and radiotherapy, or other newer modalities, applicable as well to pulmonary small cell carcinomas, are the treatments of choice.

PARAGANGLIOMA

Laryngeal paragangliomas take origin from paraganglionic tissues normally found in the larynx. The paraganglia of the larynx are part of the branchiomeric paraganglionic system and are distributed in a paired, bilateral fashion in relation to laryngeal arteries and nerves.¹¹ A superior pair is found in the anterior one

third of the false vocal cords in relation to the superior laryngeal artery and nerve and next to the superior margin of the thyroid cartilage.¹¹ The inferior pair of paraganglia are typically found near the cricoid cartilage, either between it and the thyroid cartilage or between the cricoid and the first tracheal ring.¹¹ The associated neurovascular structures are the inferior laryngeal artery and nerve. Neurovascular relationships with paraganglia are further underscored by the occasional findings of paraganglionic tissues within recurrent laryngeal nerves.¹¹ Smaller, aberrant or accessory paraganglionic tissues within the larynx have also been described. Barnes,¹¹ after a critical review of the world's literature through April 1990, rejected 44 of the 78 reported laryngeal paragangliomas. This indicates surgical pathologists are either unfamiliar with the lesion when it occurs in the larynx or they have been presented with biopsy specimens that lack the features found in extralaryngeal paragangliomas (Fig 3A). Endoscopic biopsy forceps compression of the tissues may play a role by obscuring expected histologic findings. The misdiagnoses have taken two directions: a misinterpretation of an atypical carcinoid as a paraganglioma or, conversely, overcalling a paraganglioma to a higher-grade neoplasm. As a consequence, the comparatively benign paraganglioma has acquired an unjustified poor prognosis.

The paraganglioma is the only laryngeal neuroendocrine neoplasm with a female preference (3:1 over males).¹¹ The supraglottis (principally the right aryepiglottic fold-false vocal cord region) has accounted for 82% of the tumors.¹¹ Fifteen percent have been subglottic and 3%, glottic tumors.¹¹ There are no documented examples of clinically functional or multiple (extralaryngeal) forms.¹¹

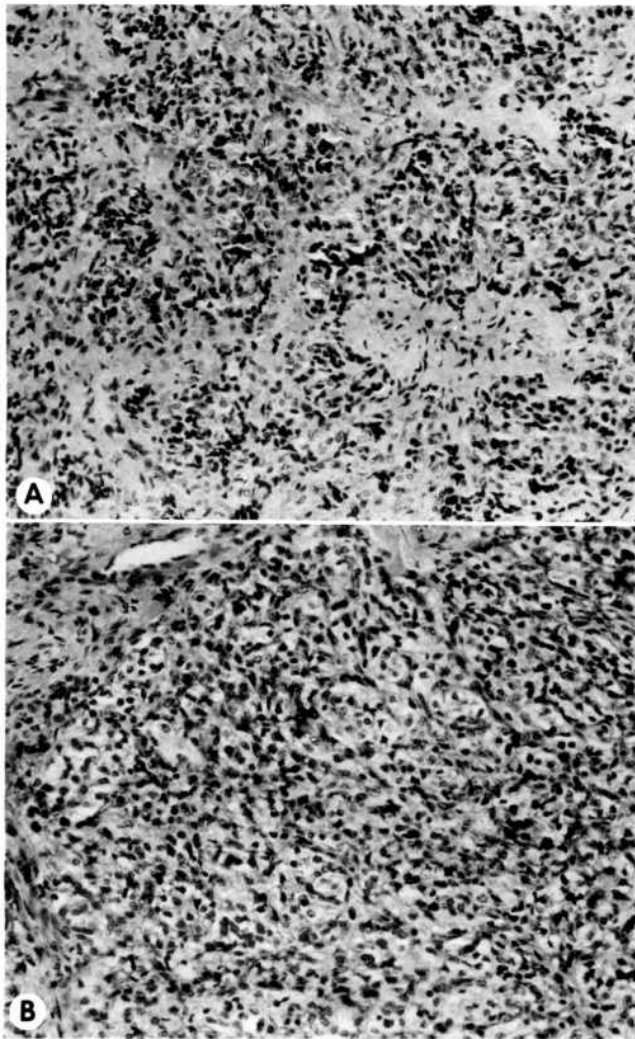


Fig 3. Paraganglioma of larynx. A) Biopsy specimen (H & E, original x120). Compression artifact and fibrosis obscure diagnostic features. B) Photomicrograph taken from section of tumor removed by partial laryngectomy (H & E, original x160). Organoid clusters of chief cells are much more evident than in biopsy specimen of same tumor, shown in A. C) Stained to demonstrate sustentacular cells (black cells) with immunostaining for S-100 protein antigen (original x200).

Circumscribed and at times manifesting a "capsule," paragangliomas of the larynx in optimum histologic preparations do not differ from paragangliomas at other anatomic sites. They are vascular tumors composed of chief and sustentacular cells in an organoid, alveolar, or *Zellballen* arrangement (Fig 3B). Sustentacular cells are often few in number and may be absent. The chief cell's cytoplasm varies from optically clear to vacuolated or amphophilic. Mitotic figures are rare. The tumors are argentaffin-negative but are argyrophilic with a Grimelius silver stain. Immunocytochemical reactions are like those for other paraganglionic tumors of the head and neck, ie, nearly always reactive with antibodies against neuron-specific enolase, chromogranin, and S-100 protein antigen (sustentacular cells). Most studies indicate an absence of calcitonin and cytokeratins. In electron optic examinations, the chief cells manifest desmosomelike bodies but without insertion of tonofibrils.¹¹ They also contain membrane-bound, dense-core, 120- to 200-nm neurosecretory granules.

The clinical behavior of any paraganglioma, in-

cluding laryngeal, cannot be judged on the basis of its histomorphology. A paucity of immunocytochemical antigen expressions and few sustentacular cells may (Fig 3C) portend an aggressive behavior.¹¹

Surgical removal of some form (local, cryosurgery, supraglottic, or total laryngectomy) has been the mainstay of treatment. Local recurrence, usually attributed to incomplete removal, has been recorded in 17% of the cases accepted by Barnes.¹¹ Only 1 of 34 paragangliomas has metastasized.¹¹ This low metastatic rate ranks these paragangliomas with jugulotympanic tumors and behind those of the vagal and carotid bodies.

The classification presented in Table 1 fulfills the pathologist's need for "pigeonholing" neoplasms, and it is undeniably a necessary guide to diagnosis and management. Nonetheless, it has to be appreciated that the epithelial neuroendocrine neoplasms exist in a continuum and that transitions can be seen between typical and atypical carcinoid and between atypical carcinoid and small cell neuroendocrine carcinomas. The biologic behavior then becomes that

TABLE 2. CONTEMPORARY "PROFILE" OF NEUROENDOCRINE NEOPLASMS OF LARYNX

	<i>Typical Carcinoid</i>	<i>Atypical Carcinoid</i>	<i>Small Cell Neuroendocrine Carcinoma</i>	<i>Paraganglioma</i>
Gender (M:F)	12:1	3:1	4:1	1:3
Peak age incidence	50 to 60 y	50 to 60 y	50 to 60 y	45 to 60 y
Site of predilection	Supraglottis (submucosal)	Supraglottis (submucosal)	Supraglottis (submucosal)	Supraglottis (submucosal), preponderantly on right side
Usual method of treatment	Surgery, including laryngectomy	Unsettled; surgery with or without radiotherapy	Conservative surgery with multimodality treatment	Surgery
Behavioral characteristics	Metastases to regional lymph nodes unusual; distant metastases in 4 of 13 reported cases (30%); death attributed to neoplasm in 1 of 13 patients (7.5%)	Metastases to regional lymph nodes frequent (43%); distant metastases in 44%; metastases to skin and subcutaneous tissues in 22%; 50% mortality rate	Metastases to regional lymph nodes at first presentation in 50%; 2- and 5-year survivals of 16% and 5%, respectively; nearly 75% of patients die with widespread distant metastases	Local recurrence in 17%; distant metastases in 1 of 34 patients (3%)

of the less differentiated part. In that light, it is no wonder that ancillary testing by different investigators yields inconsistent patterns. Electron optic evidence of neurosecretory-type granules may be scarce or absent. As a result, the anticipated argyrophilia may not be present. Also correlating with a low level of phenotypic differentiation is the possible finding

of cells null-reactive to keratin or neuroendocrine immunocytochemical markers. On the other hand, both neuroendocrine and epithelial differentiation may be coexpressed within a given tumor.

Table 2 presents a clinicopathologic profile of the neuroendocrine neoplasms of the larynx.

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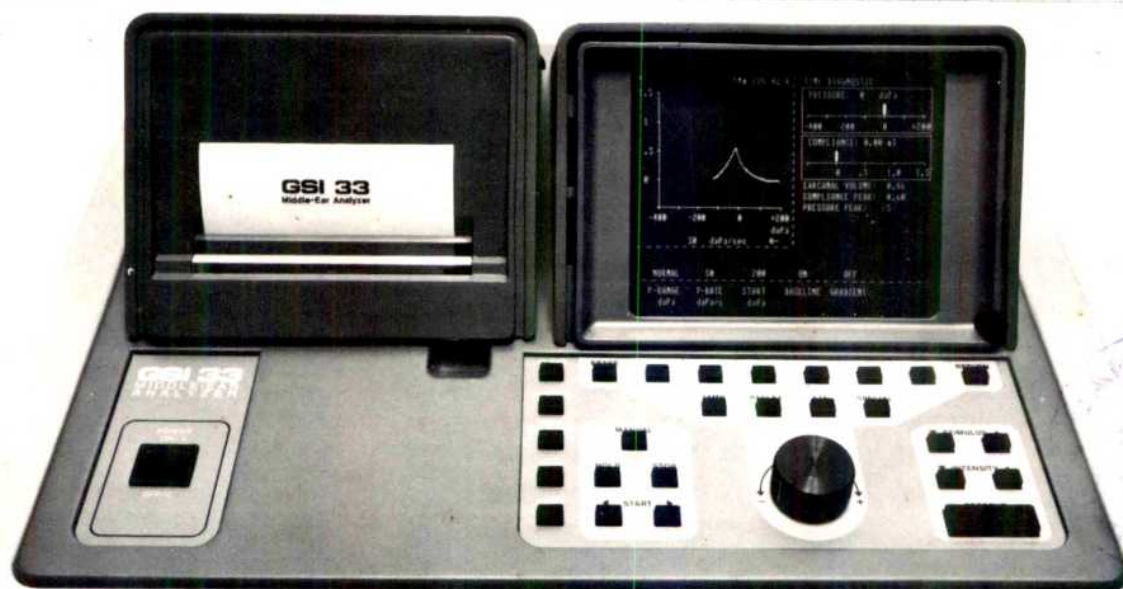
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- Reflex Threshold
- Reflex Decay
- Eustachian Tube Function Testing

For more information contact:



Lucas Grason-Stadler, Inc.
537 Great Road, P.O. Box 1400, Littleton, MA 01460
Tel: 508-486-3514, Fax: 508-486-8059, Twx: 710-347-6892

**There's No Substitute
for the Best!**

... and You Can Choose

Operators have a choice of using the preprogrammed test parameters or of selecting their own criteria via the user keys. A raised, eye-level CRT clearly displays test parameter choices and the possible alternatives. Compliance and pressure meters are on the screen with a digital readout shown continuously. Test results are displayed in real time and then summarized below the meters. Up to 8 screens can be stored in memory and recalled for viewing prior to printout. A built-in printer provides permanent records.

The innovative probe houses both Ipsi and Contra transducers. This unique probe was designed for patient comfort, ease-of-seal and accurate test results. Eartips compliment the probe, and are color coded for rapid selection of size.

Individualized probe mountings:

- Lightweight shoulder mounting (shown)
- Optional clothes clip mounting
- Optional operator wrist attachment for screening tests



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☐ Please send me the GSI 33 brochure.

☐ Please arrange a demonstration.

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